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Imaging the Beams Eye View in External Beam Radiotherapy: Geometric and Dosimetric Precision

Thesis submitted for the degree of Philosophiae Doctor

Oslo, June, 2012
The Six Scripts: Principles of Chinese Writing

“Were I to await perfection, my book would never be finished”
(Thirteenth-century Chinese scholar Tai T'ung)
Acknowledgements

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Oslo, June 2012.

Viggo Eilertsen
List of papers

This dissertation is based on and includes the following papers listed below:


II. Eilertsen K 1997 Automatic detection of single MLC leaf positions with corrections for penumbral effects and portal imager doserate characteristics *Phys. Med. Biol.* **43** 1023-1040

III. Sund T, Eilertsen K 2003 An algorithm for fast adaptive image binarization, with applications in radiotherapy imaging *IEEE Transactions on Medical Imaging* **22**(1) 22-8


Summary

In the early 1990’s the ready access to CT images for treatment planning, the advent of new beam limiting devices and electronic imaging technology on the external radiation treatment machine, challenged the existing methods and modes of working in a busy radiotherapy department. This spurred a comprehensive research activity in the Norwegian Radium Hospital with emphasis on image processing, analysis and communication. The aim was to improve the geometric and dosimetric precision of radiotherapy.

The research of the present thesis has addressed imaging in the Beams Eye View (BEV) geometry. In this geometry the investigations carried out were focused on the formation of digitally reconstructed radiograms (DRRs); methods for semi-automated comparison of electronic portal images (EPIs), acquired on the patient exit side during treatment, with the corresponding DRR; analysis of the geometric performance of the beam limiting devices; and the assessment of patient dose from the exposure of the imaging devices. These efforts were initiated shortly after the introduction of each new technology.

More specifically the present thesis treats the creation of full and limited range DRRs from CT, PET, and MR images with a quality tailored for the purpose of multimodality visualization and image registration. Furthermore, methods for extraction of image features from low contrast EPIs to facilitate automatic matching with DRRs were investigated and implemented. Another important activity has been to investigate and put into use methods for monitoring the MLC performance. This has been achieved by developing methods to accurately identify the positions of the individual leaves from portal images.

The methods developed were embedded into a hospital verification and record system. Results from the image comparisons were used in a statistically based analysis to correct the patient set-up. The lessons learned from use of the image processing tools have provided the confidence needed to introduce new advanced treatment techniques.

This comprehensive system has, since the introduction, been used to analyse more than 200 000 portal images acquired at repeated treatment sessions on 6 treatment units creating a large database of patient set-up deviation data. The use of this database and the interplay with the different professions involved has been instrumental to our understanding of the nature of the various uncertainties in play and how to assess and mitigate these uncertainties. This has facilitated sound decision making in everyday routine, and the clinical “best practice” has moved from the cm scale to the mm scale.
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### Abbreviations

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<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>2D</td>
<td>Two dimensional</td>
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<tr>
<td>3D</td>
<td>Three dimensional</td>
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<tr>
<td>4D</td>
<td>Four dimensional</td>
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<tr>
<td>ART</td>
<td>Adaptive radiotherapy</td>
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<td>BIOART</td>
<td>Biologically adaptive radiotherapy</td>
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<tr>
<td>BEV</td>
<td>Beams Eye View</td>
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<tr>
<td>BTV</td>
<td>Biological target volume</td>
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<tr>
<td>CBCT</td>
<td>Cone-beam Computed Tomography</td>
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<td>CT</td>
<td>Computed tomography</td>
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<tr>
<td>CTV</td>
<td>Clinical target volume</td>
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<tr>
<td>DD</td>
<td>Dose difference</td>
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<tr>
<td>DICOM</td>
<td>Digital Imaging and Communication in Medicine</td>
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<tr>
<td>DGRT</td>
<td>Dose guided radiotherapy</td>
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<tr>
<td>DRR</td>
<td>Digitally reconstructed radiogram</td>
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<tr>
<td>DTA</td>
<td>Distance to agreement</td>
</tr>
<tr>
<td>EBRT</td>
<td>External beam radiotherapy</td>
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<tr>
<td>eNAL</td>
<td>extended No action level (protocol)</td>
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<tr>
<td>EPI</td>
<td>Electronic portal imaging</td>
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<tr>
<td>EPID</td>
<td>Electronic portal imaging device</td>
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<tr>
<td>EUD</td>
<td>Equivalent uniform dose</td>
</tr>
<tr>
<td>FDG</td>
<td>$^{18}$F-fluro-2-deoxyglucose</td>
</tr>
<tr>
<td>GTV</td>
<td>Gross tumour volume</td>
</tr>
<tr>
<td>Gy</td>
<td>gray (unit of dose)</td>
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<tr>
<td>IBV</td>
<td>Image based verification</td>
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<td>IGART</td>
<td>Image guided adaptive radiotherapy</td>
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<td>IGRT</td>
<td>Image guided radiotherapy</td>
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<td>IMAT</td>
<td>Intensity modulated arc therapy</td>
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<td>IMRT</td>
<td>Intensity modulated radiotherapy</td>
</tr>
<tr>
<td>kV</td>
<td>kilovolt</td>
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<tr>
<td>linac</td>
<td>linear accelerator</td>
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<tr>
<td>MIP</td>
<td>Maximum intensity projection</td>
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<tr>
<td>MLC</td>
<td>Multi leaf collimator</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
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<td>---------</td>
<td>--------------------------------------</td>
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<tr>
<td>MR</td>
<td>Magnetic resonance</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>MRS</td>
<td>Magnetic resonance spectroscopy</td>
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<tr>
<td>MV</td>
<td>megavolt</td>
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<tr>
<td>NAL</td>
<td>No action level (protocol)</td>
</tr>
<tr>
<td>NRH</td>
<td>Norwegian Radium Hospital</td>
</tr>
<tr>
<td>NTCP</td>
<td>Normal Tissue Complication Probability</td>
</tr>
<tr>
<td>OAR</td>
<td>Organ at risk</td>
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<tr>
<td>PACS</td>
<td>Picture archiving and communication system</td>
</tr>
<tr>
<td>PDI</td>
<td>Portal dose image</td>
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<tr>
<td>PET</td>
<td>Positron emission tomography</td>
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<tr>
<td>PDDI</td>
<td>Predicted portal dose image</td>
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<tr>
<td>PTV</td>
<td>Planning target volume</td>
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<tr>
<td>ROI</td>
<td>Region of interest</td>
</tr>
<tr>
<td>RF</td>
<td>Radio frequency</td>
</tr>
<tr>
<td>R&amp;V</td>
<td>Record and verification (system)</td>
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<tr>
<td>SAL</td>
<td>Shrinking action level (protocol)</td>
</tr>
<tr>
<td>SPECT</td>
<td>Single-photon emission computed tomography</td>
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<tr>
<td>TCP</td>
<td>Tumour Control Probability</td>
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<tr>
<td>TI</td>
<td>Therapeutic index</td>
</tr>
<tr>
<td>US</td>
<td>Ultrasound</td>
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<td>VMAT</td>
<td>Volumetric modulated arc therapy</td>
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1. Introduction

1.1. Cancer and the principles of radiobiology in radiotherapy

Cancer is the term used for diseases where the cells of the body become abnormal and divide without control ultimately leading to the formation of tumours. The origins of cancer are not fully understood, but there are a number of known carcinogens that are involved in causing cancer. These are commonly divided into three classes: chemical carcinogens such as dioxins and tobacco smoke, physical carcinogens such as ionizing and ultraviolet radiation, and biological carcinogens such as certain viruses. The carcinogens inflict damages or changes to the DNA of a cell, producing mutations that may initiate carcinogenesis. When this happens, cells do not die from programmed cell death (apoptosis), and new cells form without being needed (inactivation of tumour suppressor genes). Cancer cells may invade nearby tissues and spread throughout the body via the bloodstream and lymphatic system (metastasis).

In the Norwegian population of 4.9 million inhabitants, 27520 new cases of cancer were registered in 2009: 54% were among men and 46% among women. Between the five year periods 2000-04 and 2005-09, the incidence rate increased by 7% in men and 3% in women. There are however large variations between the different cancers [1]. The stronger focus on cancer from the health care system and increased attention regarding cancer from the patient, screening programs, as well as an increased quality of treatment have improved the survival. The latter can be illustrated by the number of Norwegians that are alive after having had a least one cancer diagnosis: This number increased from 140 000 in 1999 to nearly 200 000 in 2009. An improved survival is observed within all the four major cancers: breast, prostate, lung and colorectal cancer.

Radiotherapy is next to surgery and chemotherapy the major treatment option for cancer. Around 40-45% of cancer patients will require radiotherapy at some point during their disease – either as the sole treatment modality or in combination with surgery and/or chemotherapy. There is a delicate balance between the anticipated control of the tumour and the complications inflicted on the normal tissue for a given radiation dose. This balance is illustrated in figure 1 where a typical example of the Tumour Control Probability (TCP) and Normal Tissue Complication Probability (NTCP) as functions of cumulative dose, are plotted. Increasing the cumulative radiation dose increases the local control (i.e. TCP), but will at the same time increase the risk of normal tissue damage (i.e. NTCP). The term therapeutic window describes the difference between the tumour control dose and the normal tissue tolerance dose [2]. In other words, there must be a dose difference between the two curves for
radiotherapy to be beneficial. Evidently, the larger the separation, the more favourable radiotherapy is. The therapeutic index gives the tumour response for a fixed level of normal tissue damage [2]. In curative cancer treatment, the key issue is to find ways of improving the therapeutic index. The relative change in this index – and to which cost - is often used to evaluate whether a new treatment procedure would be beneficial or not.

Figure 1 Illustration of a situation where the therapeutic window is in favour of radiotherapy: For a given radiation schedule and technique, a high probability of tumour control (TCP) can be reached at a dose level that does not inflict severe normal tissue complications (NTCP). The therapeutic index (TI) gives the tumour response for a fixed probability of normal tissue damage (e.g. 5%).

For many cancers the therapeutic window appears to be very narrow. The history of radiotherapy with a curative intent has demonstrated that it is a very demanding task to administer total cumulative doses that can provide the desired level of tumour control without inflicting intolerable levels of normal tissue damage. The tumour control observed in a patient population for a given type of radiation treatment is hardly ever “100%”. In fact that as many as 18% of cancer patients are likely to die with, and partly from, locoregional treatment failures [3]. This large number clearly illustrates the importance of improving the therapeutic index. Improving the dosimetric and geometric precision of external beam radiotherapy is important to achieve this goal because higher precision can increase the therapeutic index. This is the essence of the presented thesis.
1.2. The Beam’s Eye View in radiotherapy

External beam radiation therapy (EBRT) rests on the combined utilization of a) the armamentory of medical imaging modalities to produce three dimensional image volumes that represent different properties of the tissues, and b) a nearly point-formed source of high energy X-rays, electrons or heavier charges particles. Imaging modalities in common use are Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and Positron Emission tomography (PET) and recent reviews of their roles in radiotherapy are given by P. Evans [4] and U. Nestle et al [5].

A prerequisite for treatment success is high sensitivity in the delineation of the tumour and accuracy in the subsequent irradiation of the tissue, i.e. the dose deposited and the extent of the tumour must coincide at all treatment sessions. To assure and maintain the desired geometric and dosimetric accuracy as well as precision, the Beam’s Eye View (BEV) and related imaging applications have played instrumental roles in clinical practice since the dawn of radiotherapy; from the early 80’s also utilized within the framework of digital imaging in radiotherapy [6-11].

The BEV facilitates an accurate one-point perspective projection of 3- or even 4-dimensional image data sets. The position of the beam source is utilized as vanishing point defining a conical geometry identical to that of the treatment beam. The BEV therefore lends itself to the creation of accurate 2-dimensional renderings of patient anatomy suitable for use in treatment planning in particular. Looking along the beam, either by integrating information or by extracting relevant parameters from the volumetric image information, a condensed overview of the disease extension as well as the presence of critical tissues along that beam, is provided. Hence images created using the BEV perspective provide an intuitive basis for the delineation of target volumes and the subsequent shaping of the fields to be used for treatment.

Historically the BEV notion has been exploited on the treatment simulator where the combined use of an X-ray image intensifier to produce a live image feed, the exposure of a radiographic film, and possibly clinical palpation, allowed for the manual formation of treatment fields. A typical example of a simulator image is found in panel A of Figure 2 including the outline of the treatment field.

In modern radiotherapy planning the borders of each single radiation field can be derived from a circumscription of the Gross Tumour Volume (GTV) [12] as depicted in the BEV, with a polygon shaped structure. The projections of these polygons into the body will define for each treatment session the volume actually treated and the dose distribution inside
it. This perception is valid for the most simplistic types of treatments such as the use of a single field to the most sophisticated types of treatments involving volumetric intensity modulated arc therapy (refer to section 1.6).

Likewise, the advent of new imaging technology and digital image processing methods in the beams eye view provide valuable means to reveal and characterise a number of properties vital to the quality of treatment execution. These include the geometrical precision of patient set-up and treatment unit mechanics, as well as the precision of the treatment beam fluence and the dose delivered in the patient.

1.3. Digitally Reconstructed Radiograms

In radiotherapy planning an important BEV application is the creation of the Digitally Reconstructed Radiogram (DRR) [8, 13-16]. The DRR is formed by integrating the image voxel values along the paths of divergent rays that emerge from a common focus and hit an imaginary detector plane at the centres of each detector (image) pixel. By selecting the beam source as focus point, the DRR and BEV geometries coincide. A novel algorithm for the creation and exploitation of DRRs are presented in Paper I with a few extensions demonstrated in section 3.10 of this thesis. A typical example is found in panel B of Figure 2.
After treatment planning has been carried out, the real irradiated volume is defined by the number, shapes, and directions of the beams. The relationship between this volume and the tumour is readily conceived by means of the DRR. With the advent of sophisticated 3-dimensional imaging, the DRR images may comprise a superposition of a multitude of disease related aspects vital to the potential success of the treatment plan being designed, ranging from tumour extent, its localisation and elasticity with respect to the patient skin, to tumour physiological characteristics that may stem from for instance PET or functional MR images (diffusion, perfusion, hypoxia). Furthermore the DRRs can visualize various technical aspects of the treatment plan as for example the individual beamlets used to modulate the intensities of the beams, the resulting dose distribution in the patient in a slice perpendicular to the beam, and the temporary location and movement of beam shaping devices. In addition, the DRRs facilitate a synoptic display and visual verification of the use of safety margins around the treatment target and organs at risk; margins that are appended to encompass various uncertainties related to planning and treatment execution. The algorithm and software described in Paper I can be used to realize many of these displays by making possible a combination of planning and imaging information from different modalities.
1.4. Electronic Portal Images

Another key use of the BEV geometry is found in portal imaging and the formation of the electronic portal image (EPI) in particular [17]. A portal image usually denotes an image acquired using the radiotherapy beam. This image can be used to verify the patient set-up during treatment. Historically, portal images were created from the exposure of radiographic films located on the beam’s exit side of the patient. During the 90’s electronic portal imaging devices (EPIDs) were invented. These devices have by and large replaced the use of films and exhibit several advantages compared with films. Various types of EPIDs have been developed, based on different optical and x-ray detector systems [18].

First of all EPIDs generate high resolution digital images of high quality that are immediately accessible at the treatment unit via dedicated image display and processing software. This allows for on-line patient set-up error detection and correction as well as more comprehensive imaging regimes to be implemented, both during the treatment session as well as throughout the course of treatment. To start with, EPIs thus replaced portal films as a means to measure the localisation of the patient anatomy with respect to beam edges, i.e. to ensure that the tumour is indeed being irradiated taking the applied margins into account. The processing and analysis of EPIs for the detection, geometric control and verification of both the beam limiting devices as well as the set-up of the patient during external beam therapy, has been a major development activity within the present work ([19], Paper II and III). This work resulted in a commercially available product marketed under the acronym IBV (Image Based Verification, Nucletron BV).

Another important quality assurance aspect of radiotherapy is to determine the dose delivered to the patient during treatment. Quickly after the advent of EPIDs, the idea of portal dose imaging was investigated by several research groups. It was early on shown that EPIDs, and EPIDs made from amorphous silicon (a-Si) in particular, can act as convenient tools that can comply with the requirements of a dosimeter [20-26]. In this dissertation, some concepts of EPID dosimetry and a method for estimating transmitted dose from EPIs, or rather Portal Dose Images (PDIs) were studied in Paper VI.

EPIDs are usually manufactured as an integrated part of the treatment machine. This makes image acquisition and assessment a lot easier and more efficient compared with films. The advent of EPIDs has therefore stimulated an evolving research activity in designing and developing EPI processing and analysis methods. This effort has continued to date and paved the way for the concepts of Image Guided Radiotherapy [27-28].
1.5. Imaging in the Beams Eye View of MR and PET

Recently, MR scanners dedicated for radiotherapy treatment planning have been introduced. The superior soft tissue contrast of MRI over CT makes this imaging modality particularly appealing as delineation of tumours presumably can be carried out more accurately. This has created a desire to develop methods to calculate dose distributions based on MR images alone in order to supersede the traditional planning CT [29-33]. The dosimetric accuracy of this approach for the radiation therapy planning of prostate cancer was investigated in Paper VIII. Albeit MR images are well suited for planning purposes, full volumetric projection DRRs of MRI data do not result in images well suited for BEV display of anatomical structures of interest. The algorithm presented in Paper I addresses this issue by enabling range limited projections that allow for the visualization of tumour outlines in MRI based DRR (see section 3.10).

As with MRI, PET scanning has over the past decade emerged to become a valuable imaging modality that can provide both anatomical and biological tumour information of importance to radiotherapy planning [5, 34-36]. In conventional PET diagnostics, the Maximum Intensity Projection (MIP) has been used to create parallel beam 2D projections of the tumour. Evidently, the conical projection geometry is desirable for tumour visualization in radiotherapy planning. Hence, divergent beam MIPs are needed and this was investigated and realized by the algorithm of Paper I.

1.6. Radiotherapy with a linear particle accelerator

Radiation therapy eradicates tumour cells by depositing ionizing radiation energy into the patient’s body. The imparted energy (radiation dose) can damage the cells such that they loose their ability to reproduce. The probability of achieving such a response increases with dose. Evidently, the radiation directed at the tumour cells, also affect the normal tissues along the radiation path. The key intent of radiotherapy is therefore to deposit an adequate radiation dose in the tumour cells and at the same time keep the dose to normal tissue at an acceptable level - a demanding task especially in cases of deep-seated tumours.
The work horse of external beam radiotherapy used to realize this aim is the linear particle accelerator (*linac*) with an install base of more than 8000 world wide [37]. This L-shaped device (*gantry*) is designed to produce x-rays of typical energies in the range 4 MV to 25 MV. This is achieved by first accelerating electrons to near light speed through a series of microwave cavities energized by a RF power generator. After leaving the accelerating structure, the electrons are deflected a net angle of 90° by an electromagnetic field (bending magnet) and subsequently stopped by a target of solid metal (typically tungsten) thereby suffering an energy loss through the emission of high energy bremsstrahlung and heat. The exit surface of this target is designated the source of radiation. The bremsstrahlung beam is formed by a flattening filter and a series of beam shaping devices, or collimators (Figure 3). The radiation is thereby converted into a photon beam of nearly homogenous fluence applicable for treatment. Alternatively, an electron beam can be created by replacing the tungsten target and flattening filter with a scattering foil. In this case beam shaping is usually achieved with the use of an electron tubus and cutouts of sufficient thickness made from a low melting point alloy.

The gantry is mounted in such a manner that it rotates around the horizontal axis and so that the beam axis is kept orthogonal to this rotation axis. Further flexibility with respect to the incident direction of the beam is obtained by rotating the patient table. This allows for radiation to be delivered to the patient from nearly any direction. The intersection point of the gantry axis of rotation and the central axis of the beam is a fixed point in space denoted the *isocentre*. It is customary to define a right handed coordinate system – *the isocentre system* - with its origin at the isocentre. Consequently, the BEV perspective is realized by looking down at the isocentre from the beam source.
The modern linac contains a multileaf collimator (MLC) that can be used to shape the photon beam to better conform to the target volume. The MLC can also be applied to modulate the photon intensity by sweeping the individual leaves across the beam. This technique constitutes the basis of intensity modulated radiotherapy (IMRT) – a radiotherapy technique that makes it possible to deliver highly conformal dose distributions. IMRT is most commonly realized by either one of the following three methods:

- The “sliding window” or dynamic multileaf collimator (DMLC) approach. For a fixed gantry position the opening formed by each pair of opposing MLC leaves is swept across the target volume under computer control, with the radiation beam on, to produce the desired fluency profiles [38].
- The step-and-shoot, stop-and-shoot, or segmental multileaf collimator (SMLC) approach. For a fixed gantry position, a series of multilayer shapes (segments or subfields) is administered to create the fluency profile. The radiation is turned on only when the MLC leaves are stopped in each prescribed position [39].
- Intensity-modulated arc therapy (IMAT, [40]) or volumetric-modulated arc therapy (VMAT, [41]) where radiation from one or more arcs (i.e. gantry rotations) are administered. Each arc constitutes a series of irregular apertures shaped by the MLC. In addition, the output fluence, the speed of rotation, as well as the MLC orientation may be varied as a function of the gantry angle.

It must be noted that with the DMLC and SMLC approaches, several intensity modulated beams (typically 5 to 9) from different gantry angles are combined in order to create a high dose volume that conforms to the shape of the tumour.

Clearly the MLC plays a vital role in modern radiotherapy; for beam shaping and even more importantly for modulation of the radiation intensity. It has been stated that “IMRT without a MLC is like a fish without a bicycle” [42]. It is of the prime importance that the mechanical precision and dosimetric characteristics of this device are maintained at all times to ensure correct dose to the patient. The impact of the latter aspect was addressed in Paper IV, and followed up by the detailed quality control study of the long term stability of MLCs from different vendors in Paper V. Lately, the significance of EPI and EPID technology has been demonstrated in facilitating real-time DMLC tracking of respiratory moving targets during delivery of arc therapy [43-44]. The concepts presented in Paper II for detection of
single multi collimator leaves in an EPI, can very well be extended to verify that the actual
tracking of the MLC is carried out correctly.

1.7. Medical imaging in radiotherapy

High-precision radiotherapy typically consists of five major phases: Patient scanning –
treatment planning – set-up verification – beam-delivery – and response assessment. During
all five phases imaging and image technology have always played important roles. A
relentless development and innovations within this field have facilitated tremendous progress
in the ability to discern tumour from normal tissue, and new image based techniques have
been put into use to verify and even greatly improve treatment accuracy and precision. In so
doing the collateral damage to normal tissue and the risk of treatment failures due to
inadequate dose to the target have been reduced. In particular, the introduction of digital
imaging techniques and new imaging modalities such as: CT, CT simulator, MRI / MRS, MR
simulator, PET/CT, medical ultrasound (US) devices, optical surface scanners, Cone-beam
CT (CBCT), EPI, and molecular imaging, have made possible great improvements in the
quality of treatment planning, increased the precision of treatment execution, and augmented
treatment response assessment.

Dynamic imaging can be used to characterise anatomical motion (respiration,
deformation). This technique has become increasingly more important in the radiotherapy
process over the past few years. Likewise physiological properties (e.g. metabolic or
functional activity) of the tumour before, during and after treatment can be assessed by
dynamic studies such as 4D CT or PET and MR/MRS. The latter may sometimes be further
supported by tumour biopsies and/or other invasive measurements of tumour characteristics.
The aim is of course to make use of this information to enhance the geometric and dosimetric
precision as well as the treatment efficacy, and to gain knowledge of tumour response. This in
turn can be utilized to further optimize treatment quality.

Three-dimensional medical images reflect different properties of the tissues and organs
in the body. The basic geometric unit is a volume element (voxel) that is specified by its
dimensions in the x-, y-, and z-directions. These voxels are usually organized in a cuberille,
and an image displays a cut-plane through this volume. The voxel values and images,
respectively, may represent:

- The linear X-ray attenuation coefficients (CT images).
  - The images exhibit a detailed view of the anatomy and form the basis for dose
calculations and planning.
Pathology may show up as increased or decreased attenuation values, changes in morphology and/or enhanced uptake of contrast media.

- The activity concentration of a radioactive compound (SPECT and PET images).
  - The images represent physiological processes in the tissues because the radioactive compounds enter biological pathways (e.g. uptake of radioactive glucose as part of the cell metabolism, or phosphonate compounds as building blocks of bone tissues).
  - Pathology may show up as increased or decreased uptake.

- The magnetic resonance properties of the tissues or artificial contrast media (MR images).
  - The signal strength depends on the relaxation properties of protons in the tissues and the images provide excellent soft tissue contrast.
  - The images can provide measures of perfusion by the accumulation and clearance of contrast media.
  - In addition the images may provide a measure of proton diffusion coefficients.

- The characteristics (resonance peaks) of the NMR spectrum (MRS, CSI)
  - Reflect the concentration of metabolites.
  - Pathology and aggressiveness may show up as changes in the ratio between such concentrations.

- The magnitude of the reflected signals from longitudinal high frequency acoustic waves by the tissues (3D US images)
  - Doppler measurements of blood flow.

**Molecular imaging** is an aggregated term including in vivo imaging of labelled biomolecules typically within the field of nuclear medicine including PET. Examples of the application of such molecules include:

- Targeting angiogenesis (the formation of tumour blood vessels) using radioactive compounds that may bind to structures present in the recently formed new blood vessels.

- The detection of sub-clinical tumour tissues by radioactive labelling of antibodies or receptor homing molecules and subsequent imaging of their concentration in the vicinity of the tumour.

- Imaging of tumour proliferation with use of radioactive labelled amino acids (methionine, thyrosine), and imaging of hypoxia by quantifying the uptake of for example $^{64}$Cu-ATSM or $^{18}$F-MISO, respectively.
The importance of the above mentioned development has brought about a number of new buzz-words to the field. Image Guided Radiotherapy (IGRT) [27-28, 45] usually refers to image guidance techniques used at the time of treatment to guarantee that the CTV receives the prescribed dose, and/or that irradiation of critical structures is avoided. Some of the image-guided methods, portal imaging for instance, are more suitable for imaging rigid bone structures as encountered in the head and neck and pelvic regions. By exploiting the spatial localisation of the tumour with respect to these structures, an indirect verification of tumour position relative to the beams is achieved. Other techniques, like US, X-ray fluoroscopy and possibly also CBCT, are able to localise soft tissue tumours and even determine non rigid setup variations and movements such as in the case of prostate and lung cancer [46-48]. Tumour surrogates like gold markers [49-50] have been introduced as a means to mitigate the lack of adequate soft tissue contrast in EPIs and CBCTs.

Lately it has become common to broaden the scope of the term IGRT to encompass imaging for planning and treatment follow up as well. An example of the latter would be Dose Guided Radiotherapy (DGRT) that includes methods to retrospectively calculate the real dose distribution delivered to the patient in a treatment session. This dose can be obtained from EPIs where the image intensity is converted into transmitted dose to give portal dose images (PDIs) [20-26]. By back projection of these dose images onto a CBCT image volume acquired prior to the actual treatment session, the 3D dose distribution delivered to the target and to the organs at risk, at the time of treatment, can be estimated [51]. By comparing this single session dose distribution to that of the treatment plan, discrepancies in dose delivery can be detected and potentially mitigated (see below). Furthermore, a fraction by fraction record of the “true” dose accumulated in the tumour and normal structures can be established. The outcome of both IGRT and DGRT can be utilized to adapt the treatments to the measured daily variations in patient set-up, patient contour, the internal tumour position as well as tumour shape and size. New treatment plans can be created that compensate for the observed discrepancies for instance in dose delivery. In this manner uniformity in doses administered in a population of patients is enhanced. Eventually, such increased dose uniformity may improve the ability to measure and discriminate the effect of dosimetric and non-dosimetric factors on tumour and healthy tissue outcomes in clinical trials. By collecting IGRT/DGRT data from many patients, a more precise determination of treatment-specific tumour control and normal tissue complication probabilities, respectively, can be attained. This ongoing use of imaging to monitor, update and adjust the treatment is known as Image Guided Adaptive Radiotherapy (IGART) [52-54].
The ultimate goal is however to move from this population based knowledge to the application of individual patient-level biological information in order to design and carry out the optimal therapy for that individual. This type of personalized treatment strategy is called radiation theragnostics [55] (from Greek *therapeia*: to treat and *gnosis*: knowledge). Theragnostic radiation therapy and imaging involves a process where the aim is to go from a usually uniform dose prescription (applicable to a group of apparently similar patients), to a voxel-directed prescription of a non-uniform 4D dose distribution based on functional or molecular image information that reflect the biological characteristics pertinent to radioresistance or radiosensitivity as outlined above. The latter approach is often described as *dose painting by numbers* and is seen to be designated the aggregated term Biologically Adapted Radiotherapy (BIOART) [56-58].

1.8. Treatment volume delineation and visualisation in external beam radiotherapy

The first aim of radiotherapy planning is to identify and differentiate cancer cells from normal tissue to produce a delineation of the Gross Tumour Volume (GTV). High sensitivity of the techniques involved in carrying out this task is paramount for a successful treatment outcome. As outlined previously, a number of sophisticated imaging techniques can be applied to facilitate this process. Likewise, a high specificity is of importance to evade excessive side-effects from irradiation of normal tissue.

The resolution limit of modern 3D imaging is typically of the order 1 mm, and microscopic extensions of tumour cells below this limit are hard to discern clinically by imaging or other examinations. It is therefore customary to make use of a margin around the GTV in order to define a Clinical Target Volume (CTV) [12]. The magnitude of this margin will depend upon tumour characteristics and can vary depending on tumour-site and histology. Ultimately, advanced functional imaging systems correlated with image-registered pathological specimens will allow one to learn more about the true extent of the disease compared to the functional or physiological image; in particular to separate out normal tissue from disease at the tumour periphery and thereby reduce the uncertainty related to the sub-clinical spread. When it is not possible to determine the CTV margin with reasonable accuracy, the margins must remain generous and conformal avoidance methodology could and should be deployed to spare critical normal structures.

In addition, the accuracy and precision of external beam radiotherapy is deteriorated by inter- and intra-observer variations in the definitions of GTV/CTV, as well as an
uncertainty in the position of the CTV with respect to the direction of the treatment beams during treatment [59]. The latter is inherent to the way in which radiotherapy is carried out, and is caused by internal organ motion that may displace the CTV relative to its planning position, alterations in the CTV shape, as well as day to day variations in the actual set-up of the patient. As a result, the margins are further expanded to encompass these inaccuracies to give the Planning Target Volume (PTV) [12], and a treatment plan conformed to the PTV must be created to ensure proper dose coverage of the CTV throughout the entire course of treatment.

The above mentioned uncertainties and the margins needed to mitigate the effects, pose a problem as the irradiated volume inevitably will include healthy tissue. This unwanted side-effect should of course be minimized, but finding the optimal margins for the treatment of a particular patient in question is an intriguing challenge. Margins recipes based on the analysis of population based uncertainties have been presented [59-63], and in Paper VII this issue was investigated and a model to define the optimal CTV-PTV margin was presented.

Despite tremendous advances in cancer care and within radiotherapy in particular, both technically and clinically, it is in many cases still challenging to achieve local cure or local tumour control. This anomaly may be summed up by the following statement (credited to the Canadian medical physicist Harold Johns): “If you can’t see it, you can’t hit it, and if you can’t hit it, you can’t cure it.” The great achievements that have been made to the physical aspects of radiotherapy, i.e. the ability to accurately calculate and subsequently sculpt a 3D dose distribution inside the body has, as of yet, not necessarily been translated into improved cure rates even when these methods entail use of higher doses. This may be attributed to the fact that radiotherapy is still for a large part an evidence-based form of medicine. The detailed knowledge about the tumour’s response to radiation in individual patients, and the microbiological tumour characteristics that may affect this dose response, are still unknown or inaccessible to clinicians. We know that radiation works, particularly for a population of patients with a similar diagnosis, but not exactly why or how, and this shortcoming can evidently lead to occasional treatment failures. Lately, the advent of molecular imaging and the conception of a biological target volume (BTV) [58] have gained footing as a viable notion for addressing the above mentioned contradiction.

In this context imaging in the Beams Eye View holds promise to play an important role in order to shorten the gap between physical and biological realms of radiotherapy. The BEV has the potential to provide a detailed and intuitive (over)view, along the rays of radiation, of a very complex scene that contains a multitude of information objects, spanning
from the anatomy and physiology of the tumour and surrounding healthy tissue, to radiation
dose and tissue response; from a geometrical as well as a temporal point of view.
2. Applications of digital imaging and image processing for the investigations and assurance of treatment precision: The evolving aims

The first set of aims for the present work was formulated as early as 1992. A common denominator has been the exploitation of digital imaging and image processing techniques to capture, create, and analyse information contained in BEV projections. Due to the rapid technological and scientific development in the fields of portal imaging, image processing and image communications, the aims were extended several times. However, the overall aim has always been to improve the precision in external beam radiotherapy.

Many of the technical inventions that form the basis for the present work have been investigated a short time after they have been introduced into the market and thus reflect central aspects of the development in this field. The present dissertation is based on developments conducted by the author and the research papers published as part of this work. The main part of the software produced in the projects was written by the author.

In parallel with the investigations, it has been an overall goal to continuously implement the ideas in the forms of applications that could be put into use in the busy clinical environments of the radiotherapy department. Additional efforts have been required to address and solve the real problems that inevitably emerge when such methods are used to analyze images of thousands of patients.

This has necessitated the design and development of a comprehensive system that can provide efficient and reliant access to the vast amount of digital images produced for each patient, as well as to provide means to convey the results of the image analysis to the treatment personnel. As part of this strategy, new standards for digital image communication have been investigated, adapted and implemented to facilitate the desired work- and data-flow.

The aims of the BEV based development were to augment the planning sensitivity (i.e. the ability to adequately enclose the entire tumour in the high dose volume) and specificity (i.e. the ability to avoid normal tissue irradiation) when it comes to preventing real geometric and dosimetric misses during therapy. These aims and modes of operation hold the potential to improve local control and hence lead to better cure rates.
3. A comprehensive Beams Eye View based system for image workflow, processing and analysis for routine use in a large scale radiotherapy department: Development and implementations conducted by the author.

Image processing and analysis tools are often developed as part of an academic research effort. When these computer codes are to be used routinely in a large radiotherapy clinic, they must be embedded into computer programs suitable for running in a distributed environment available to the various groups of the radiotherapy staff. Ideally, these programs should be intimately linked with a system that can administer the huge amount of images and associated information created each day. On the other hand: the practical testing of such programs in such an environment will reveal errors and problems and thus spur further development of both the program codes, methodology, and the supporting IT infrastructure. When successfully implemented, the new possibilities created will presumably lead to improved precision in the radiotherapy practice.

This chapter sketches the historical development of BEV based image processing for patient set-up verification, image analysis of precision of equipment-dependant performances, and how these efforts were linked with the development that lead to the presented comprehensive system. The main aspects of this development were:

- Method for fast generation of high quality of DRRs (Paper I)
- Methods for image segmentation (Paper III) and registration [19]
- Methods for detection of single MLC leaves in EPIs and the quality control of MLCs (Paper II, IV and V)
- Comprehensive infrastructure to support image and data workflow in the radiotherapy department [64-67]
- Developments of systems for managing routine statistical evaluation of patient set-up errors and embedding the image analysis software in a record and verify system.

The historical development is sketched as a background and as an instructive learning phase, but the solutions presented here are derived from work that was carried out over a period of 5-7 years.
3.1. Historical background and motivation for the presented development

In the Norwegian Radium Hospital (NRH) the geometric accuracy of the patient set-up was historically addressed by a visual inspection and qualitative comparison of radiographic portal and simulator films, respectively. Typically, this was carried out by manually measuring the distance from the field borders, as depicted on the two films respectively, to bony structures. As a rule of thumb, discrepancies of the order 5 mm or less were considered acceptable. Evidently, this was an inaccurate approach because it was subjective and insensitive to more subtle deviations in the patient set-up. In addition, the work-load and slow speed related to film development and handling of heavy film cassettes hampered extensive use of this modus operandi. Basically, this approach served as a “one-shot” verification and documentation of the treatment fields at the start of treatment, and may have prevented gross treatment errors or adverse events. It could not facilitate realization of the accuracy considered necessary in modern conformal radiotherapy of curative intent. Here a persistent set-up precision of the order of 1 mm (translations) and 1° (rotations) would be desirable to minimize the margins and adverse effects on healthy tissue.

The advent of EPIDs and digital portal imaging provided new image processing abilities and spurred a development of computer-assisted techniques. Digital images lend themselves to frequent use of quantitative image analysis methods for the detection and subsequent correction of deviations in the patient position. Obviously, the accuracy of the analysis tools should match or even supersede the observed clinical distributions of random and systematic deviations in the patient set-up (see section 3.3).

A project initiated at the Norwegian Radium Hospital in 1992 aimed to make image based verification an integrated part of the daily clinical routine in order to improve the accuracy and precision of radiotherapy. A part of this project was to investigate and develop techniques for automating the image registration process [19]. Initially this study addressed the comparison of digitized simulator and portal films. As the use of CT images for treatment planning and EPIDs became commonplace during the mid 90’s, these image modalities were replaced by the use of DRRs and EPIs, respectively, and these modalities became the focus of further research efforts in the project. DRRs rather than digital simulator images were considered to be the most reliable type of reference image since they were based on the actual treatment planning data. Early on in the project a demand emerged for DRRs other than those provided for by the planning system. A development commenced with the aim to provide a flexible program and user interface from which the user could specify different image quality measures depending on the final clinical use of the DRR. At an acceptable speed, high quality
DRRs should be formed that could visualize soft tissue and bone, and in which different anatomical features could be distinguished. A first version of a DRR algorithm was completed by the author in 1996 and soon put into clinical use. Since then, the algorithm has been further improved and new functionalities have been added (paper I and section 3.10).

3.2. Digital image communication and networking

The access to efficient computer systems and networking architectures were considered necessary prerequisites for the realisation of optimal image based verification. Such technology is indispensable in order to fully exploit the vast amount of information offered to the oncologist by the various imaging modalities. In this context the network comprised the technological infrastructure needed to support a seamless connectivity and integration of radiotherapy equipment (e.g. imaging modalities, treatment units) and patient information systems (e.g. hospital information systems, electronic medical records, treatment planning systems, record and verify systems, Picture Archive and Communication Systems).

![Diagram](image)

**Figure 4** Illustration of the early server/client DICOM data- and work-flow solution developed as part of the NRH project. A query retrieve (Q/R) Service Class User facilitated search and transfer of DICOM data, and a storage service class provider / user (SCP/SCU) facilitated local storage as well as push/pull of these items to/from a local DICOM directory. A graphical user interface (GUI) made possible input of the basic search and retrieve elements such as patient ID, image acquisition date, and selection of which network application to interact with.

The NRH project therefore also aimed to address data- and workflow related aspects of electronic portal imaging in order to promote and facilitate the integration of this new imaging modality into the clinical routine (Figure 4) [64-67]. This involved the establishment of a long term strategy for exploiting and implementing new standards for digital image communication.
and archiving in medicine (e.g. DICOM and PACS). Alongside these initiatives, a development of custom made interfaces to extract images from vendor specific image databases were considered necessary as intermediate solutions.

The clinical use of standards for networking and image communication has in recent years been addressed by the IHE-RO initiative (Integrating the Healthcare Enterprise – in Radiation Oncology) endorsed by several professional organisations in the field [68]. The various IHE-RO committees unanimously promote the application of existing standards for data communication and storage (e.g. HL7, DICOM) when it comes to the development and implementation of new solutions. Within this context, various IHE-RO working groups have outlined a number of clinically relevant use cases (workitems) that demonstrate desired workflows (profiles) and corresponding inter-operability that vendors should adhere to when releasing new products. A vendor commitment to IHE-RO defined protocols would hence smooth the integration of devices from different manufacturers in a multi-vendor environment.

A suite of computer programs were developed as part of the NRH project. An important design aspect was to maintain a modular programming code that readily could be adapted to different system architectures, operating systems and computer environments as well as to comply with the IHE-RO recommendations. A high level programming language was used to allow for easy integration of the programs with existing clinical computer systems. This facilitated a fairly trouble-free transition from a dedicated system running in-house, to a suite of programs that later on was embedded into a commercial radiotherapy record and verify (R&V) system [69].

3.3. Selection of methods for the first radiotherapy image registration efforts in the Norwegian Radium Hospital

A discrepancy between the intended (DRR) and measured (EPI) position of anatomical structures relative to the field border – attained by comparing these BEV images - is considered a set-up error. It is customary to assume that the origin of this error is an unintended translation and/or rotation of the patient pose relative to the direction of the beam (i.e. machine coordinate system). The fundamental challenge in this context is to deduce this translation and/or rotation from the measurements in the BEV, and furthermore to estimate a shift and/or rotation of the patient support system to mitigate the incorrect set-up and thereby maintain the planned treatment accuracy. An alternative approach would be to redesign the
treatment plan to account for the altered pose, but for a number of technical reasons this has not been a viable option until recently [70-71].

A critical prerequisite in this context is to know the relationship between the geometry of the BEV images and the patient support system, and furthermore to transform the BEV images into one common coordinate system in order to facilitate a comparison of image intensity patterns in the two images (a process commonly denoted image registration). Likewise, image similarity measures must be established and applied to quantify the degree of correspondence in the set-ups as depicted in the DRR and EPI, respectively. Several intermediate steps are usually carried out as part of this process, and different approaches and methods (presented below) have been developed in the NRH project to resolve these issues.

3.3.1. Field shape matching to establish a transformation into one common coordinate system

In theory, an accurate quantification of the location and orientations of the EPID with respect to the treatment table (or patient) would make possible a direct conversion of the measures derived from the EPI into a corrective table shift. This would require an absolute and minute calibration of the position of the EPID relative to the isocentre. However, most EPID attachments, especially those that were available in the early days of the EPI era, are made subject to sag, wear and tear in the suspension. The effects of such abrasions may jeopardise the precision of this procedure.

An alternative and more flexible approach that is independent of the EPID position was selected for the NRH project. This method involved matching the location and orientation of the collimators, depicted as the field edge in the portal images and as the field border in the reference image (e.g. DRR or simulator image), respectively. The field border, representing the planned outline of the beam, was constructed from a combination of the positions of the field shaping devices defined in the plan prescription. The aims of this field shape matching are two-fold: First to verify the shape of the treatment field, and secondly, to establish the geometric transformation (magnification, translation, and rotation) between the EPID and the reference image coordinate systems, respectively. The relationship between the coordinate system of the reference image and the patient support system can usually be established from the treatment plan. This implies that by application of the derived transformation, a set-up discrepancy detected in the EPI can be translated into table shift values.
Since this procedure involves the use of the field edge of the EPI, a robust and fast method for field edge detection was developed taking into account the response characteristics of different EPIDs. Initially edge detection was carried out applying an implementation of the Mexican hat or generalized Laplacian operator [72] (Figure 5, upper row). This is a rotational invariant operator where noise suppression and edge detection can be achieved with the use of one convolution kernel only. The zero-crossings of this operator response in the beam penumbra were found to correspond very well with location of the dosimetric field edge. However, the lack of information of gradient direction with this method would sometimes lead to loops (false edges) when trying to chain the zero-crossings into a continuous field edge outline. Therefore, a method based on the Canny edge detector was implemented and replaced the Mexican hat scheme [73] (Figure 5, lower row). The EPI is first convolved with a Gaussian filter to reduce noise. Then the image intensity gradients in the horizontal and
vertical image directions are approximated by a convolution with Sobel operators. The horizontal and vertical responses are combined into a gradient magnitude image as well as into an image holding the gradient direction. Only if the gradient magnitude assumes a local maximum in the gradient direction, the corresponding image pixel is defined to be on the field edge (non-maximum suppression).

The field shape matching was carried out applying a chamfer matching technique [74]. More specifically, a polygon that represented the field border was superimposed on a distance map created from a binary image that represented the field edge (Figure 6). The root mean square average (r.m.s.) of the pixel values in the distance image that coincided with the polygon, was used as the measure of correspondence. The search for the set of geometrical transformation parameters that minimized the r.m.s. was carried out using a simplex downhill technique [75].

![Figure 6](image)

**Figure 6** The geometric transformation (i.e. translations, rotation and magnification) between the coordinate systems of the reference image (panel A) and portal image (panel B), respectively, is found applying a chamfer matching technique: The polygon representing the field border in the reference image (red outline) is superimposed on the Euclidean distance map of a binary image representing the field edge (indicated by the white outline in panel C). The root mean square average (r.m.s.) of the pixel values in the distance map that coincide with the red outline, is used as a measure of geometric fit. Panel D illustrates this concept. A simplex downhill technique is used to minimize the r.m.s. value (panel E). The geometric transformation that minimizes the r.m.s. is defined as the position of the best fit (panel F).
Evidently, field shape matching as such is an intermediate step. The program was therefore implemented with no need for user interactions, but allowed for a visual inspection of the end result. In hindsight, the method has proven to be very fast and reliable and only a few minor changes have later been introduced.

3.3.2. Image segmentation, registration and fusion

The geometric transformation that came out of the field shape matching was used to put the DRR and EPI into one common geometrical frame of reference. Further image registration based upon a direct application of image-intensity techniques, was made difficult by the inherent differences in the physical aspects of the image formation including differences in EPID technology: DRRs were created with high tissue contrast and in such a manner that anatomical landmarks could easily be discerned and extracted. Electronic portal images on the other hand usually have a low tissue contrast because of the high energy of the X-rays (typically 4-25 MV) that are used for creating the images (compare for instance panel A and B in Figure 6). The latter can make it hard to visually distinguish the anatomical structures or fiducial landmarks in the EPIs that are relevant to the set-up verification process, and the comparison of the EPI with the DRR can be error prone and time consuming.

An important goal of the NRH project was therefore to develop computer assisted EPI contrast enhancement and segmentation techniques as a desirable pre-processing step to facilitate the image registration. The ultimate aim was to reduce the need for user interaction to a minimum (i.e. make the process less subjective) and thereby improve the accuracy and precision of the registration result.

The aim of image segmentation in general is to subdivide an image into constituent parts or objects that display similar characteristics. Typically this implies the identification of image regions of pixels that adhere to some predefined statistical or morphological patterns defined globally and/or locally. The extracted Regions of Interests (ROIs) are usually identified either by a description of the boundary that encloses the region, or by the image coordinates of the pixels that belong to the ROI.

In this context the goal was to extract homologous features from the two images (e.g. DRR and EPI), and subsequently to devise a distance measure that could be used to estimate the degree of mismatch between these features. The coordinate transformation that minimizes (or maximizes) this distance is then applied to evaluate the correctness of the patient set-up. The parameters used to model the coordinate transformation between the two datasets depend
on the modalities involved and the clinical site. In the simplest situation, it is only necessary to account for differences in patient orientation (pose) at the time of imaging. For rigid anatomy, such as the skull and pelvis, only three rotation angles ($\phi_x, \phi_y, \phi_z$) and three translations ($t_x, t_y, t_z$) are usually needed to describe any deviations in the pose. The presence of image distortions or mis-calibrated imaging devices would require more degrees of freedom such as anisotropic scaling ($s_x, s_y, s_z$). However, this really is a quality control issue of the EPID, and it is customary to assume that such effects are corrected for prior to image registration. Evidently, the situation becomes more difficult when the anatomy involved is not rigid (i.e. deformable). In such cases a more complex spatially and temporally variant transformation involving a larger number of degrees of freedom is required to register the data properly. The latter type of registration of medical images is a very active area of investigation. Elastic registration methods based upon for instances measures of entropy have been implemented in clinical applications [76-77]. In the case of the 2D images considered here, only the rotation angles $\phi_x$ and $\phi_z$ can be measured and was included into the metric.

![Figure 7 Illustration of different image segmentation techniques: Panel A shows original EPI. Panel B shows a binarised version A after unsharp masking. Panel C shows the original EPI. Panel D shows a binarised version of C after local adaptive thresholding](image-url)
Initially it was, however, decided to only consider rigid transformations and to disregard rotations. The latter was motivated by the fact that only translational discrepancies could easily be corrected for clinically by applying couch shifts.

A number of techniques for image enhancement and automated feature extraction were implemented and tested as part of the NRH project development [4, 19]. The outcome of the techniques developed can be categorised into three classes of increasing data complexity: point features, curve features, and template features. Examples of point features are manually placed fiducials, projections that represent recognizable points in bone anatomy, or (implanted) radio-opaque markers (e.g. gold markers in the prostate). Examples of curve features are edges (surfaces) or ridges in the projection of bony anatomy, grey value medial axes, or simply the projected contours of the radiation field edge. Examples of template features are regions of pixel values that contain one or more projections of anatomical fiducial structures. Template features provide more information for image alignment than point or curve features and may consequently be applicable to a larger range of treatment sites.

In the NRH project templates created from the high intensity ridges formed behind the crests of bones were chosen as the most appropriate image features since these are present in both EPIs and DRRs. Curve and point features were thus inherently supported. An unsharp masking technique (Figure 7, panel B), the use of a gradient operator and global thresholding and subsequent thinning were used to extract the ridges from the images [19]. Later on a local adaptive binarization (Paper III) was introduced as a simpler, faster, and more robust procedure (Figure 7, panel D). This preprocessing allowed for an implementation of both semi-automated and fully automated template based matching.

![Figure 8](image)

**Figure 8** Illustration of cross correlation to establish the translation between the two templates of the DRR and EPI, respectively. Panel A: Before correlation. Panel B: Illustrates the correlation function where the position of the peak value is used as a measure of displacement. Panel C: After applying the translation values corresponding to the position of the cross correlation peak.
In the NRH project this was initially achieved applying a cross-correlation approach [19] (Figure 8) and later improved by a method based on chamfer matching. The latter is illustrated in Figure 9 demonstrating the sequence of operations involved: Extraction of a structure template from the DRR (panel A), the transferral of this template to the EPI applying the field shape matching transformation matrix (panel B), and finally the establishment of the geometric set-up deviation using chamfer matching (panel C). In this case a binarised version of the EPI was fit to the distance transform of the structure template of the DRR. The latter panel shows a superposition of the match results based on 25 image registrations.

Figure 9 Illustration of automated DRR-EPI registration for quantification of patient setup deviation: 
A. DRR with anatomical landmarks. B. Corresponding EPI with extracted structures (red) and the landmarks transferred from the DRR superimposed (green). C. Distance transform of the structures in A superimposed with the matched position of the structures from B after chamfer matching. D. The position(s) of the treatment beam based on the measured the set-up deviations of 25 consecutive treatment sessions.
3.4. The first system: RTNavigator; design and workflow considerations

The system that was developed, the RTNavigator, was planned and implemented to include the methods outlined above. The designed workflow comprised the following sequence of operations:

1. Import of treatment planning data and corresponding images; either by the use of an in-house developed DICOM query and retrieve and/or storage service class provider program package (Figure 4), or by proprietary data mining of vendor specific databases utilizing Open Database Connectivity (ODBC) application programming interfaces (API).

2. Automatic detection of the field edge in the portal image and field outline in the simulator image, respectively.

3. Automatic extraction of anatomical fiducials in the portal and simulator images, respectively.

4. Matching of the field shapes in order to establish the geometric transformation (i.e. magnification, location, and orientation) between the EPID and isocentre coordinate systems, respectively, providing a transform matrix.

5. Use of the transform matrix to position the fiducials from the simulator image correctly in the portal image with respect to the portal image field edge.

6. Application of cross correlation to match the location and orientation of these fiducials in order to disclose possible rotation and/or translation of the patient set-up. This operation results in a quantification of the patient set-up deviation (in the coordinate system of the EPID).

7. Use of the transform matrix to convert the deviations into isocentre coordinate system units (millimetres).

8. When possible combine set-up deviations from orthogonal beams to compute the lateral, longitudinal and vertical table shifts that are required to correct the observed set-up errors.

9. Systematic storage of measured set-up deviations and image registration data.

It was decided to present set-up errors on-line in the patient support coordinate system whenever possible, to facilitate corrective actions, i.e. translations and/or rotations of the treatment couch. The latter was carried out manually by the staff at the treatment unit.
3.5. Clinical experience and further development of the RTNavigator

The demonstrated usefulness of the RTNavigator programs and the associated image analysis methods motivated further steps to be taken in order to implement their use into the clinical routine. In parallel with the in-house developments, advances in treatment delivery techniques (e.g. IMRT) along with an increased scientific activity on the international scene exploring the use of EPIDs in other domains such as dosimetry, encouraged us to continue the development. In addition, feedback from users and conference discussion contributed significantly to new ideas and improvements in the design of the system. These fruitful discussions and clinical experience gave rise to the following RTNavigator enhancements:

- The precision of the field shape matching was improved by extensive dosimetric characterisation of the EPID response and development of an algorithm for precise detection of the corresponding field edge.
- The precise positions of the individual leaf tips and flanks of the MLC were detected by a tailored EPI processing technique developed for that purpose (Paper II).
- A database system for long term storage of images and deviation data resulting from each treatment session was designed and implemented, intimately linked to the R&V system.
- The deviation data stored in the database were used for longitudinal follow up, and an analytic tool was developed to discriminate between random and systematic set-up deviations from sliding average calculations.
- From a combination of detected set-up deviations derived from the acquisition of orthogonal EPIs, the required corrective table top translations were calculated.
- The demand for robust and reliant automatic matching spurred actions to further sophisticate the pre-processing of the images involved. This processing comprised of image segmentation (binarization), ridge detection and adaptive histogram equalisation (Paper III).
- In treatments where the field extended outside of the EPID, a routine was developed to clip the planned field outline to comply with the edge of the EPID. By this technique erroneous field shape mismatches were avoided.
A few remaining issues or weaknesses were identified, and there were no reliable solutions developed within this project to resolve these. The most important ones were:

- The DRR/EPI matching technique, even with combined use of orthogonal EPIs, did not enable the detection of rotations around the patient’s lateral and longitudinal axes, respectively. This was caused by a geometric degeneracy intrinsic to the method and can lead to incorrect set-up error measures as rotations can be misinterpreted as translations.
- The automatic extraction of ridges in the EPI and/or subsequent template matching on occasions displayed unacceptable high failure rates primarily caused by very low contrast detail in the EPI. As a consequence, the outcome of the template matching would require user verification on a regular basis.
- Field size errors (not field shape errors!) could not easily be detected because any difference in magnification between the EPID and isocentre coordinate systems was determined intrinsically in the field shape matching procedure.

3.6. The second system version: Image Based Verification - IBV

During the early days of the RTNavigator development and the introduction of EPIs in radiotherapy, we experienced a lack of an adequate infrastructure to manage image registration results and a longitudinal monitoring and handling of systematic and random deviations. This made it difficult to fully exploit the new possibilities provided by EPI and to implement efficient measures in daily routine to reduce the impact of set-up errors. The apparent answer to this issue was to intimately integrate the RTNavigator with the hospital radiotherapy Record and Verification (R&V) system (VISIR, Nucletron BV). The R&V system is the sole source of planning/set-up data during treatment execution and provided an appealing framework for conveying corrective actions derived from the EPI analysis. In cooperation with Nucletron BV a commercial version of the RTNavigator was implemented and designated the acronym IBV (Image Based Verification). The IBV module, made ready for sale in 2003, supported the following functionality:

- Scheduling of portal image acquisition according to predefined protocols, and subsequent image retrieval and automatic import of acquired images using DICOM.
- Scheduling of image based patient set-up verification and approval according to various action level strategies.
- Semi-automatic 2D image registration applying template matching - including a workflow manager to guide and visualise the intermediate steps of the image registration process.
(e.g. preparation of the reference image, portal image field edge detection, field edge match, anatomy match and the presentation of the results).

- Trend analysis of image registration results including techniques for combining the match results from the analysis of multiple fields at different gantry angles.
- Scheduling of patient reposition requests (i.e. table movement) based on the outcome of the trend analysis, either by prescribing new relative table coordinates (fully automatic procedure), or by a translation of patient skin marks (manual procedure).

By December 2011, the IBV was in daily clinical use on 6 treatment machines at the Norwegian Radium Hospital. On average roughly 100 pairs of images have been registered for set-up analysis every day for the past 8 years amounting to more than 200 000 image based set-up verification procedures handled by the system.

3.7. Imaging, set-up correction strategies, and trend analysis

The potentially ample access to meticulous measurements of patient set-up deviations made possible by EPI, created a need to consider and conceive cost efficient imaging and set-up correction strategies. It is common to describe set-up deviations as the combination of a systematic and random quantity. The systematic component represents the recurring difference between the intended and actual set-up, whereas the random component represents the fluctuation in the set-up deviations that is typically observed during each session. The total set-up deviation is therefore the sum of the systematic and session specific component and gives rise to a frequency distribution of set-up deviations over all sessions. The systematic set-up deviation is characterised by the average value of this distribution whereas the random component is often characterised by the corresponding standard deviation.

In this context, the concepts of off-line and on-line verification protocols have been introduced to deal with the measured set-up deviations [78-79]. In the case of an on-line protocol images are acquired at the beginning of each treatment session applying just a minor (negligible) part of the fraction dose. While the patient is awaiting treatment completion, the image analysis takes place. An on-line correction protocol will thus reduce the impact of both systematic and random set-up deviations. Evidently, this is a time critical process as a proper corrective action (e.g. shift of the treatment table top) must be established and take place as soon as possible after image acquisition. Otherwise inevitable random disturbances in the patient pose or target volume position will undermine the benefit of the procedure. In addition, this method is work-load intensive and costly as patient throughput is lowered.
With an off-line correction protocol, images acquired during treatment are analysed after the completion of a treatment session, and a sliding average is calculated from the measured deviations. The intention of this approach is to attain an estimate for the systematic component and apply this estimate during subsequent sessions, thereby neglecting the impact of the random component. Statistically, the power to extract the systematic from the random component increases with the number of image acquisitions (at different sessions). This may seem a paradox considering the clinical desire to reveal and mitigate the systematic set-up errors as soon as possible after treatment start. Off-line protocols will include an increasing number of images and related analysis results as the treatment progresses. These should be considered in conjunction in order to deduce reliable measures of corrective action based on statistical evaluation of the image registration results. The latter aspect represents a logistical challenge in which workload and expediency must be balanced against imaging frequency.

In the IBV system this issue was addressed by facilitating the use of two different action level strategies published in the literature. The Shrinking Action Level (SAL) [78] and extended No Action Level (NAL, eNAL) [79-80] protocols provided the necessary tools to unveil systematic set-up errors by the utilisation of frequent imaging (analysis) early in the course of treatment followed by (typically) weekly imaging.

In the SAL protocol a predefined threshold value that scales with the inverse square root of the number of measurements, is used to determine whether a given set-up deviation is to be corrected, i.e. to distinguish a random from a systematic set-up error. This threshold value can be obtained from a retrospective study of the set-up precision of a patient population that undergoes a site specific treatment regiment.

In the eNAL protocol a correction obtained from the average set-up discrepancy is executed when a predefined number of measurements (typically 3) have been acquired, and is subsequently followed by (typically) weekly measurements.

The efficacy of the SAL approach was evaluated as part of this project using the RTNavigator program for a group of patients that were treated for cervical cancer. These patients were treated with two opposed beams and for the AP field and EPIs were acquired using the PortalVision system (Varian Inc, Palo Alto, USA). First one group of 30 patients where followed up by an imaging schedule that was standard clinical practice of that time, i.e. one portal image at the first treatment session. A correction was introduced if a deviation larger than 5 mm was discovered. In order to establish an estimate of the threshold needed for the use of the SAL protocol, EPIs were acquired on the next three sessions as well, but no correction action was taken. For a second group of 30 patients, images were acquired at the
Figure 10 The figure illustrates the efficacy of the SAL protocol when applied to the AP field of a group of cervix cancer patients (30 patients in each group). Panel A shows the systematic set-up deviations measured in the lateral and longitudinal directions without the use of SAL, and panel B shows the corresponding values with the use of SAL. The systematic deviations in the lateral and longitudinal directions decreased from 1.9 to 1.1 mm, and from 2.4 to 1.8 mm, respectively, with the use of the SAL protocol. The red ovals encompass 95% of the systematic set-up deviations. Panel C shows the fraction of patients (in %) that had a systematic set-up deviation above a given value (abscissa) - here given as the length of the systematic 2-dimentional displacement from isocentre (in mm). The red curve shows the results with and the blue curve without the use of the SAL protocol, respectively.

first four treatment sessions and corrective action was taken if a deviation greater than the relevant action level was observed. An initial action level of 6 mm was used (around 3 times the standard deviations of all set-up deviations found for the first group of 30 patients). The results demonstrated (Figure 10) that the use of SAL gave a reduction in the systematic deviations (defined as the standard deviation of the average of the average deviations for each of the 30 patients). In Figure 10 one can clearly see that the average of the set-up deviations in the lateral direction was not zero. In fact it was \(-1.0\pm0.4\) mm (95% CL), i.e. significantly different from zero. The underlying cause of this anomaly may have been a misalignment of the light and the radiation fields, respectively, of the particular treatment machine that was used to treat the patients studied.

Evidently, the concept of an off-line correction strategy collapses if the random component is a major contributor to the set-up deviations. In this case only on-line imaging will suffice. The choice of correction strategy may typically be a compromise from balancing of work-load related issues (image acquisition and analysis and treatment machine occupancy) and the potential clinical benefit or demands on the precision in relationship to the safety margins in use.
3.8. Imaging dose in the Beams Eye View: EPID based absolute dosimetry

The accuracy of external beam radiotherapy may be characterised by two measures: The geometric precision in the patient set-up and beam-limiting devices with respect to the tumour, and the dosimetric precision in delivered dose to the tumour. Obviously the geometric set-up precision (set-up errors) will constitute a bearing on the dosimetric accuracy, but day-to-day variations in for instance patient anatomy can have an independent impact on the latter.

The idea of converting the electronic portal imager signal into a measure of radiation dose (or dose rate) came about more than two decades ago [81]. To achieve this, the EPID must be operated in an integrating mode to capture the radiation transmitted during the entire exposure of each beam. In addition a number of different (non-imaging related) EPID specific characteristics must be established in order to attain a measure of dose within a precision of 1-2% (1 SD). Having this established, the resulting Portal Dose Image (PDI) is thus another example of applying the BEV geometry for treatment verification.

The NRH project was extended around 1999 to also include preliminary investigations on the use of EPIDs for dosimetric purposes. In the first phase the dose response characteristics of the PortalVision LC250 detector from Varian was studied in order to make possible a transformation of the EPI signal into dose per monitor unit [82]. This work included among other aspects: measurements of detector dose rate dependency, field size dependency, influence of detector cross-talk from lateral scatter inside the detector housing, influence of patient scattered radiation on detector response, individual detector element sensitivity, build-up requirements, and long term stability (Figure 11).

In the next phase, a previously developed formalism [83] was elaborated that enabled the calculation of dose to a water equivalent phantom located in the position of the EPID to a depth equivalent to the thickness of the EPID. The aim of the calculation was thus to facilitate a prediction of the portal dose transmitted to the EPID behind the patient, i.e. to create a Predicted Portal Dose Image (PPDI). The work in this study comprised extensive testing of the validity of the formalism and the model for transforming EPI signal into PDIs – the PDI representing the dose per monitor unit - as well as the testing of a concept based on a gamma analysis [84] for the comparison of PDIs and PDDIs. A dedicated module was implemented and made part of the RTNavigator to allow for a conversion of EPIs into PDIs, and to report the distance to agreement (DTA), the dose difference (DD), and the combination of these to form the a common measure – the gamma index – in order to facilitate a comparison of the PPDI with the corresponding PDI. The latter would represent a sophisticated method to verify
correct dose delivery and patient set-up. The results of this work are reported in Paper VI of the present thesis.

![Graph A: Dose rate response, 6MV photons](image)

![Graph B: Field size dependency, 6MV photons](image)

![Graph C: Long term stability, 4MV photons, Clinac 600C](image)

![Graph D: Illustration of various dose response characteristics established for the Varian LC250 EPID](image)

**Figure 11. Illustration of various dose response characteristics established for the Varian LC250 EPID:** Panel A shows the EPID dose rate response for a 6MV beam. Panel B shows the EPID field size dependency for a 6MV beam. Panel C shows EPID long term stability for a 4MV beam. Panel D shows a comparison of a dose profile of a PDI (solid line) and the corresponding profile measured with an ion chamber located inside a mini phantom (dotted line).

Recently, methods have been developed to back project the PDI into the patient anatomy applying either CBCT images or the planning CT images, and compare the resulting dose distribution with the planned [51, 85]. Further investigations into this area were beyond the scope of the present thesis.

### 3.9. Imaging in the Beams Eye View for quality control of the Multi Leaf Collimator

The electromechanical aspects as well as the clinical use of the MLC have rapidly evolved since the early 90’s when the MLC was given a commercially acceptable design and became readily available [86-87]. In modern radiotherapy the multi-leaf collimator of the linear
accelerator has become instrumental to the formation of the sophisticated dose distributions by for instance arc IMRT [88]. The first treatment machine equipped with a MLC was put into clinical use at NRH late 1992 (one of the first of its kind world wide).

The BEV provides an intuitive basis for investigating the MLC performance since the principal path of operation of the MLC is orthogonal with respect to the central axis. The overall shaping of the radiation field, the accuracy and precision of speed and location of the individual leaves can be studied utilizing this viewing geometry. This also applies to the dosimetric properties. As a part of the NRH project development of methods to detect and monitor the position(s) of the collimator leaves was initiated around 1995 exploiting the new possibilities provide by EPIDs. The results of this early work are outlined in Paper II. The methods developed for a dosimetric correct detection of the field edge from the electronic portal images and determination of each single leaf position, were included in the RTNavigator software and also made part of the commercial IBV release.

By 2005 the MLC had become the standard field shaping device on the majority of treatment machines in the department, and IMRT was being introduced as the preferred treatment technique for patients receiving radiotherapy for cancer in the head and neck region. The MLC systems were subject to a mechanical quality assurance program that included a meticulous calibration of the individual leaf positions. However, this procedure contained elements of visual assessment by the staff at the treatment unit that could induce systematic errors of the order 1-2 millimeters. Such errors could potentially have an impact on the delivered dose distributions for treatment techniques that contained a large number of smaller treatment fields, such as the IMRT plans that started to emerge in the clinic. A study was therefore initiated to investigate the consequences of such errors. Radiographic films were exposed in the BEV perspective to investigate the sensitivity of systematic leaf calibration errors on the delivered dose distributions. The films were subsequently digitized using the scanner software developed in the early years of the NRH project, and the gamma analysis software of the RTNavigator used to analyse the results. The findings are presented in paper IV.

The principal ideas and learning experiences of the works of paper II and IV initiated a need to investigate the reproducibility and long term stability of the MLCs from the three vendors of linacs installed in the hospital. The results of this work are described in paper V, and the concepts and software that were developed to analyse stripe test images presented in that work are still in use in the clinic.
3.10. Extended development and use of the DRR algorithm

A full projection DRR represents a condensation of the 3D anatomical information and inherently some important features may be obscured by the overlaying structures. The properties of the DRR should be adapted to its intended use. A DRR should clearly depict bony landmarks and fiducials implanted to facilitate patient set-up verification and avoid other structures that can disturb an automated image registration procedure. Furthermore, for the DRR to be used as a means to ensure sufficient coverage – and avoidance of critical organs - both the tumour and all critical organs should be displayed. This also means that information from other kinds of images (MRI, PET/SPECT) should be visualized. The above requirements were the background for the extensions of the DRR functionalities presented in Paper I.

DRRs originating from different modalities can be formed and displayed by image fusion and visualization techniques using a geometry that lets the central ray (or central axis of projection) always pass through the isocentre of the treatment plan. Through the intimate integration of the RTNavigator - and later on IBV - with the R&V system, this detailed set-up information was made readily available to the DRR program that was developed. The treatment field outline together with the position of the central ray constituted both a visual and a physical frame of reference for the BEV/DRR display. Depending on the context, these custom made DRRs were shown either side by side or with several types of image information superimposed in one display.

Prior to or during the projection that forms the DRR, it is possible to manipulate the 3D image information in the following general ways:

- **Preprocessing** of the 3D image volume to enhance the visibility of certain structures or tissue classes of interest. This can be carried out in a number of ways e.g. by the use of different transfer functions or intensity mappings.
- **Segmentation** of organs of interest such as bone, kidneys, heart, liver, intestines, tumour, or by the use the image subtraction techniques such as subtract pre-contrast image from a contrast image [89]. Segmentation may also include the use of volumes of interest imported from the treatment planning system.
- **Limitation of the range** of the image volume that is projected. The purpose is to remove the disturbing effect of overlaying (over-projected) tissues. Typically the range can be defined to include only the tissues in the volume surrounding the tumour.
- **Formation of maximum intensity projections (MIP)** e.g. to check that all the tissues that have accumulated 18F-FDG have been included in the treatment field.
The present version of the DRR algorithm can without modification be used for all the purposes described above, and the technical details of the implementation is described in paper I. Since the programs were written in a 4 generation language, additional modifications are feasible when required. In Figure 12 a few examples of the use of these new functionalities of the DRR formation are illustrated. As frames of reference and to facilitate visual comparison the following overlays may be included:

- the location of the beam limiting devices and central axis,
- segmented gold markers, and
- segmented organs (lung, urinary bladder etc) or tumours.

**Figure 12** Illustration of the visualisation possibilities of the extended version of the DRR algorithm: Panel A-C displays three different beams eye view projection of the CT images of a patient that was given stereotactic radiotherapy to a tumour in the lung. Panel A shows a bone enhanced DRR. Panel B shows a combined range limited bone and lung/soft tissue enhanced DRR. Panel C shows a range limited tumour enhanced DRR clearly visualising the position of the tumour. Panel D-F illustrates different visualisations of gold markers implanted in the prostate of a patient treated for prostate cancer. Panel D shows the frontal view of a bone and implanted gold marker enhanced DRR superimposed on an enhancement of the soft tissue of the GTV. Panel E shows a lateral view of a range limited DRR (avoiding the most lateral parts of the pelvis and the left and right femoral head) where the locations of the automatically detected gold markers are indicated. Panel F shows a lateral view of a range limited DRR superimposed on the BEV projection of the outlined CTV (red), rectum (blue) and bladder (green).
3.10.1. Imaging the Beams Eye View in combined CT and MRI based radiotherapy planning

MR images could provide reference images equivalent to the CT based DRRs. In such cases, the use of CT based simulation could be omitted [29, 31, 90]. An intermediate approach is first to coregister the MR images with the planning CT images. The registered MR image volume is then used to create MR based DRRs in the BEV geometry of the treatment plan. This would allow for image features unique to the MR modality to be combined with the standard CT based DRR without difficulty. This latter feature has been implemented by the author in the extended version of the DRR program.

Figure 13. Illustration of combining DRRs based on CT and MR images, respectively: Panel A shows a typical CT based DRR where bone has been enhanced. Panel B shows a corresponding MR based DRR when projecting the complete image volume. Panel C shows a range limited version of the image in B in order to improve the visualization of the contrast enhanced tumour. Panel D shows a combination of the image in panel A and C that can be used for set-up verification.

Figure 13, panel A, demonstrates a bone enhanced CT based DRR that is appropriate for 2D image matching. Panel B demonstrates the corresponding MR based DRR created from a full
projection of the MR volume. Even though there is a striking resemblance between image A and B, bony landmarks suitable for matching with an EPI are not as distinct. Panel C shows a range limited version of the image in B created to visualize the contrast enhanced tumour burden inside the MR volume. Finally, in panel D, the part of the range limited MR DRR enclosed by the radiation field border, is combined with image A to create an image clearly demonstrating the location of the tumour as well as the surrounding bony tissue.

3.10.2. Imaging PET activity in the Beams Eye View by divergent beam geometry MIP

Integration of FDG-PET information into the treatment planning process creates a desire to visualize the metabolic activity superimposed on the conventional DRR. In a full projection PET DRR there is an inherent danger that the uptake of FDG in healthy tissues would add up and diminish the visibility of, or even completely mask, tumour tissue (Figure 14, panel A). One method to circumvent this problem and to enhance tumour visualisation could be the divergent beam (BEV) maximum intensity projection (MIP). In a standard parallel projection MIP image, each pixel value represents the maximum intensity encountered along the parallel rays of projection. In the in-house developed DRR software, the PET MIP projection is carried as follows: First, the PET image volume is partitioned into thinner sections or slices that are oriented orthogonally with respect to the central axis of the beam. Next, intermediate DRRs from the projection of each image section is created. Finally, a PET MIP DRR is created by sampling the maximum intensity from corresponding pixels (i.e. pixels in the same locations) in the intermediate DRRs (Figure 14, panel B). This approach is still subject to testing and tuning, but appears to produce PET DRRs than can improve tumour visualisation.

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Figure 14. Illustration of DRRs based on PET images: Panel A demonstrates a full projection of the PET image volume. Panel B shows MIP projection of the same volume. Note the enhanced visibility of the gross tumour as well as positive lymph nodes. It seems that one lymph node (lower left nodule) was missed by the treatment beam. Panel C shows the DRR of the FDG uptake encompassed by the GTV that was outlined in the transversal PET images, superimposed on the corresponding CT based DRR.
Another visualisation technique that has been implemented is to superimpose the projection of the PET activity included in the tumour outlined on PET images, on the DRR created from the standard CT based DRR (Figure 14, panel C). This is used to display how the treatment beam relates to a given tumour outline defined by PET. The latter has relevance to the study of an important problem caused by the inferior spatial resolution of the PET scanner (effective full width at half maximum, FWHM, is approximately 5-6 mm) and the effect this may have on the margins. These effects lead to uncertainties in defining the edge of the tumour volume. Comprehensive investigations into this field are outside the scope of this dissertation.

3.11. Investigating a basis for the sole use of MRI for radiotherapy planning

During the last decade the role of MRI in radiotherapy has gradually moved from being a source of diagnostic information only, to become an integrated modality of treatment planning. The superior soft tissue contrast provided by MRI compared with CT makes this modality very well suited for the delineation of tumour and organs at risk. However, MR images lack tissue density information and may suffer from large geometric distortions that impede the sole use of MRI for planning. Therefore it is customary to refer the patient to both CT and MR examinations, and as described above subsequently co-register the MR images with the CT images in the treatment planning system. This procedure thus facilitates target delineation based on the MR images and beam set-up and dose calculation based on the CT images.

Clearly, a dual examination as described above may not be very cost-efficient. In paper VIII we therefore investigated the possibilities of using MRI as the only basis for dose planning alongside the DRR development that was presented above in section 3.10.1. As demonstrated in Paper VIII, work to perform a reliable segmentation of bone tissues and air pockets in the MR images would be warranted in order to make possible a calculation of satisfactory dose distributions. Ultrafast MR sequences ([90]) have demonstrated that imaging of bone structures is possible. These images may be used to create substitutes similar to CT that can facilitate the formation of bone DRRs required for patient set-up verification, and within the same frame of reference visualize the tumour (refer to range limited the DRRs shown in Figure 13). Skin markers that contain both iodine contrast/lead and fatty acids may also be used to establish reference points.
4. Summary of results

4.1. Paper I

A novel algorithm for generation of DRRs enabling multimodality, limited range and maximum intensity projections

Standard DRR algorithms as supplied by different vendors are not flexible enough to allow users to develop new modes of use of the increasing amount of image information available in modern radiation therapy planning and follow-up. To be able to implement such new modes of use, a new algorithm for creation of DRRs was developed. Flexibility was ensured through the use of a 4th generation programming tool, and the geometric and computational methods were tailored to exploit the fast vector and array processing capability of this tool.

A key feature of the new algorithm is to transform the patient and beam geometry into a coordinate system that has its origin in the isocentre. Its yr-axis is parallel to the y-axis of the patient coordinate system and its zr-axis lies in a plane defined by the focus vector and the yr axis. This means that the xr axis is parallel to the surface of the virtual detector. Image values are sampled along lines that are parallel to this xr-axis and this choice of geometry greatly simplifies and speeds up integration along the fan beam lines that end up on the virtual detector.

The present version of the algorithm allows for a large number of preprocessing options to enhance the contrast of selected tissues and other details, and information from several medical imaging modalities may be included into the same DRR. Furthermore, to be able to show details around the tumour or around a critical organ, the projection range can be set to only include these structures. The effect of removing other tissues is to get a significantly better view of the structures of interest. Another option offered by the new algorithm is the formation of divergent lines maximum intensity projections suitable for inclusion of PET and SPECT information into the BEV. Through the link to the clinical systems, treatment data including field outlines are easily imported. Field outlines serve as common reference structures for different DRRs of the same beam (scene).

4.2. Paper II

Automatic detection of single MLC leaf positions with corrections for penumbral effects and portal imager dose rate characteristics

In this paper a novel method for the detection of MLC leaf positions from electronic portal images was presented. This involved a detailed study of the fundamental properties of the
MLC and portal imaging device (EPID) such as the dosimetric characteristics of the field edge penumbra behind the leaf tips and flanges, and the corresponding signal response and distribution produced by the EPID. In particular, an image processing method was developed to identify the radiation field in the portal images from an analysis of local intensity gradients, and measurements were performed to relate this field edge to the MLC leaf tip position defined from a geometrical (light field edge) as well as a dosimetrical point of view (the 50% decrement line). These measurements showed that a correction term that depended on the leaf position was required in order to correctly relate the image intensity gradient to the light field (geometrical leaf tip position) and the dosimetric field edge. The magnitude of the correction terms varied from -0.6 to 1.2 mm. Applying the correction, the method allowed for an accurate determination of the MLC orientation (i.e. collimator angle), one standard deviation being equal to 0.5°, as well as the positions of individual MLC leaf tips to sub-millimetre precision, one standard deviation being equal to 0.1 mm. Applying the presented methods, the MLC set-up precision of a Varian Mark 1 MLC was found to be of the order 0.1 mm.

4.3. Paper III

An algorithm for fast adaptive image binarization, with applications in radiotherapy imaging

In this paper a novel method for adaptive image binarization was presented. Image binarization is one of the most important image segmentation techniques and is applied to enhance and/or extract image texture of great relevance in carrying out a range of image processing tasks such as pattern recognition or image registration. The binary image may represent an intermediate step in such an analysis, or simply serve as an end point that is less subject to user interpretation and as such facilitate a less error prone analysis process. The present paper demonstrated the use of adaptive binarization to extract bone ridges in electronic portal images (EPI) generated during external beam radiotherapy. The EPIs represent the BEV perspective of the patient set-up used to check and confirm the location and orientation of the patient with respect to the treatment beam. Adaptive binarization was also applied to improve readability of handwritten scanned referral documents used in conjunction with at teleradiology service.

The ultimate aim of image binarization is to classify each image pixel into either one of two classes – typically background and foreground. The presented work addressed two important aspects of this process, firstly the ability to adapt the classification of a given pixel to the local variations in the image characteristics, and secondly the speed of the algorithm. In
this context local image variations were described by grey level histograms calculated from the pixel values enclosed by a rectangular window that was slid across the image. The classification (or binarization) was realised by comparing the second moments of the lower (ML) and upper (MR) part of the grey level histogram, respectively, using the grey value of the window centre pixel as pivot point. The centre pixel was classified as background if ML < MR and as foreground in the case of ML ≥ MR. The use of second moments as classification criterion made possible an incremental update of the histograms each time the window was moved. In regions with a small difference between the values of neighbouring centre pixels, this made possible a very fast classification scheme, especially for small window sizes (typically less than 20x20 pixels).

The application of the “Second Moments Adaptive Binarization” (SMAB) technique to EPIs produced binary images that facilitated an intermediate visual inspection and interpretation of the EPIs, and that were well suited for a subsequent coregistration with a BEV generated reference image (e.g. a DRR) representing the planned patient set-up. The latter made possible the implementation of a semi-automatic patient set-up verification procedure. Likewise, the resulting black/white referral documents demonstrated uniform print density and excellent readability less subject to user misinterpretation.

4.4. Paper IV

Consequences of leaf calibration errors on IMRT delivery

Intensity modulation in modern radiotherapy is to a large extent facilitated by the use of a MLC, either operated in a dynamic mode (i.e. the leaves are in motion while the radiations is on) or in static mode (i.e. combination of multiple static beam segments). In either mode, it is important to maintain a high level of accuracy and precision of the leaf positioning to ensure correct dose to the patient. In this paper we addressed the impact on the dose distribution of systematic errors (i.e. all leaves are offset by the same amount) in the MLC leaf calibration. The IMRT treatment plans of four patients with cancer in the head and neck region were altered by a displacing the MLC leaf positions of all the involved segments by a fixed offset in order to study the consequences of such discrepancies. All leaves were either forwarded or retracted with respect to their planned positions by ±0.25 mm, ±0.50 mm, and ±1.00 mm, respectively, implying a maximum change in the segment sizes of ±2.0 mm. The resulting dose distributions were measured in a BEV perspective by irradiating radiographic films placed in a slab-like phantom that were oriented orthogonally with respect to the central axis.
Subsequently the optical density was converted to dose and any discrepancy between the planned and measured dose distributions were assessed by a gamma index calculation. The results showed that by using a dose difference / distance to agreement criteria of 2% / 2mm, respectively, the simulated leaf pair positioning errors studied here gave rise to detectable dose errors. When a rejection threshold of 5% was used for the fraction of gamma index values higher than 1, two out the 32 plans studied were actually rejected. Typically, an error of ±2 mm would give rise to a median dose error of 1%. In conclusion, an accuracy of 1 mm of the MLC leaf position may be required to achieve acceptable dose distributions for MLC based intensity modulation.

4.5. Paper V

The performance of multi-leaf collimators evaluated by the stripe test

In this paper we evaluated the set-up precision of MLCs from three different linac vendors (Varian, Elekta, Siemens). A method that utilized the stripe test originally developed by Chui et al [91] was implemented to monitor both the short-term as well as the long-term stability of individual leaf positions in the three systems studied. In the BEV perspective, the stripe test consisted of several adjacent rectangular MLC shaped radiation fields that were used to irradiate an imaging plate located inside a CR cassette (Agfa CR RT1.5). The plate was subsequently scanned with a CR reader (Agfa CR 25) to generate a digital image. The distribution of the optical density formed behind the resultant penumbra of the adjacent fields constituted, in the first place, a sensitive tool to visually unveil leaf positioning errors. In this study an image processing tool was developed to analyse the shape of the density profile taken along the direction of leaf travel in order to detect such errors, and to quantify discrepancies from the intended leaf tip position. The profile in the penumbral region should exhibit a nearly flat shape in case of perfect alignment of the leaves, and become increasingly more bumpy for larger discrepancies. A MLC vendor specific calibration curve was established to facilitate this analysis. The curve related the leaf positioning error to the peak deviation of the optical density from a flat profile. The results showed that the short term reproducibility of all three systems were within 0.15 mm (1 standard deviation), whereas the long-term stability differed considerably. In particular the Siemens Optifocus displayed a time-trend that gave rise to errors of the order of 1 mm.
4.6. Paper VI

Portal dose image verification: The collapsed cone superposition method applied with different Electronic Portal Imaging Devices

In this paper a method for estimating the dose response of two commercially available electronic portal imaging devices (EPIDs) were presented and tested under clinical conditions. One EPID was based upon a scanning liquid ion chamber matrix and the other on a fluoroscopic CCD camera. A calibration procedure was devised that made it possible to convert readings from the EPIDs into images with pixel values proportional to the absolute dose in a virtual water slab located in the plane of the EPID. Local response variations were corrected in the images from both systems using open field fluence maps. The acquired portal dose images (PDIs) were compared with PDIs calculated according to the collapsed cone superposition method for a three-dimensional detector model based on water equivalent build-up material. The calculation model was founded on the beam modelling and geometric description of the treatment unit and energy used for treatment planning in a kernel based system.

For the matrix ion chamber EPID the validity of the calculation method was evaluated for several field shapes and thicknesses of patient phantoms at 6 MV X-rays, and for the camera-based EPID at 6 and 15 MV X-rays. The agreement between predicted and measured PDIs was evaluated with dose comparisons at points of interest and with gamma index calculations. The average area failing the passing criteria in dose and position deviation was analyzed to validate the performance of the method. For the matrix ion chamber on average an area less than 1 % fails the passing criteria of 3 mm and 3 %. For the camera-based EPID the average area is 7 % and 1 % for 6 and 15 MV respectively. The overall agreement centrally in the fields was 0.1 ± 1.6 % (1σ) for the camera-based EPID and -0.1 ± 1.6 % (1σ) for the matrix ion chamber.

An absolute dose calibrated EPID could validate the delivered dose to the patient from a comparison of the calculated and a measured PDI. Differences between measured and planned PDI could subsequently be used to adapt the treatment plan of the remaining sessions in order to correct or compensate for the observed discrepancies.
4.7. Paper VII

Optimal treatment margins for Radiotherapy of prostate cancer based on interfraction imaging

This paper presents a method to estimate the optimal treatment margins to achieve complication-free curative radiotherapy of prostate cancer. Cone-beam CT images of a prostate cancer patient undergoing fractionated radiotherapy were acquired at all treatment sessions to study inter-fraction tumour displacement and organ deformation. The clinical target volume (CTV) and organs at risk (OARs: bladder and rectum) were delineated in the images, generating a library of 3D CTV-OAR configurations. Random sampling from the library was performed in order to simulate fractionated radiotherapy that include the effects of intra- and inter-patient variability in setup and organ motion/deformation. For each simulated patient, four treatment fields were automatically generated around the planning CTV by the use of a MLC. The treatment margin, defined as the distance from the CTV to the field border, was varied between 2.5 and 20 mm. Dose distributions were calculated by the application of a convolution method. To accumulate or track the doses to OARs (experiencing inter fraction deformations), the session specific bladder and rectum dose distributions were reconstruction in the planning CT geometry by the application of polynomial warping. The CTV (experiencing inter fraction displacement) was assumed to be a rigid body and the corresponding dose distribution were tracked using a simple translation of the session specific dose distribution. The equivalent uniform dose (EUD), the tumour control probability (TCP) and the normal tissue complication probability (NTCP) were used to estimate the clinical effect of a given dose distribution.

The simulations produced population based EUD histograms for the CTV and the OARs. The number of patients receiving an optimal target EUD increased with increasing margins, but at the cost of an increasing number receiving a high EUD to the OARs. Calculations of the probability of complication-free tumour cure and subsequent analysis gave an optimal treatment margin of about 8 mm for the simulated population.

The current work illustrates the principle of obtaining optimal treatment margins based on both tumour and normal tissue characteristics. However, a larger patient image data base must be assessed in order to estimate clinically applicable margins.
4.8. Paper VIII

A simulation of MRI based dose calculations on the basis of radiotherapy planning CT images

The superior soft tissue contrast of MR images compared to CT images has spurred the use of this imaging modality for radiotherapy treatment planning, primarily to facilitate the process of delineating volumes of interest (VOI). However, MR images as such lack tissue density information and may also suffer from various geometric distortions. These properties hamper the direct use of these images (and the associated VOIs) for dose calculation. To circumvent these problems, the MR images are traditionally coregistered and subsequently blended with a CT study acquired for dose planning. Evidently, this process is potentially cumbersome and time consuming. In this paper we therefore addressed the potential sole use MR images for planning. We investigated the effect that different segmentation strategies, and associated selection of representative uniform densities for the segmented tissues, could have upon the calculated dose accuracy as compared to a fully CT-based calculation.

This was achieved by manipulating the densities of the CT images that formed the base data of the treatment plans for 10 patients referred to external beam radiotherapy of prostate cancer. The images were segmented into water and bone equivalent tissues by a simple thresholding of the Hounsfield values. A dose calculation was then performed using the segmented images. At the same time we scored the dose volume statistics of three different volumes of interest (CTV, bladder, rectum). In doing so, we could simulate MRI based dose calculation and evade issues related to MRI tissue classifications and any impact of MR image distortions. In addition, this facilitated a point by point comparison of the dose distributions for various tissue segmentation strategies to the plan applied clinically.

The results indicated that to achieve a dose calculation accuracy of the average dose in the CTV comparable to the plan applied clinically (relative mean difference of 0.2 ± 0.2 %), the images had to be segmented into water and bone equivalent tissues, with densities of 1.03g/cm³ and 1.3g/cm³, respectively.
5. Discussion

5.1. Introductory remarks

The work presented in chapter 3 and in the papers was undertaken to investigate techniques to improve the geometric and dosimetric precision of external beam radiotherapy (EBRT). This work rests heavily on the development and implementation of image processing techniques mainly applied to the BEV geometry. In addition aspects of system architecture and network communication have been addressed. The strong focus on sophisticated computer programming was recognized as a prerequisite in order to handle the immense amount of data produced.

The present system is a result of a continuous development in the Norwegian Radium Hospital through more than a decade. The suite of methods and programs has been used to carry out quality control of beam limiting devices and patient treatment procedures. In particular, new imaging technology and the ability to - on a daily basis - assess set-up uncertainties in individual patients have brought a new understanding of the degree of precision that can be achieved with EBRT. This work has facilitated sound decision making in the everyday routine, and the clinical “best practice” has moved from the cm scale to the mm scale.

The beams eye view represents an excellent and intuitive display mode that can show images that share a common frame of reference and that can comprise a multitude of information vital to many phases and aspects of radiation therapy such as anatomy, (molecular) biology, functionality, dose, organ motion, and treatment response. The BEV provides convenient means for monitoring and visualizing discrepancies between actual and planned therapy as well as providing perceptive demonstrations of how inter- and intra-observer variability affect beam size and hence the volume of irradiated tissue.

The field of image based verification and image guided radiotherapy has matured dramatically in the years following the initial RTNavigator investigations and developments carried out by the author. Extensive scientific efforts within numerous research groups and among vendors have produced great achievements and advances in treatment quality. Below follows as an introduction a sketch of some of the weaknesses and problems of the BEV geometry. Then follows a brief synopsis of developed the most important recently technologies and methods, and their relationships to the BEV techniques.
5.2. Weaknesses of imaging in the BEV geometry

Each pixel value of the 2D image that results from a BEV projection represents the line integral of voxel values present in a 3D image volume. In the case of the formation of a DRR (full or limited range projection) this is the outcome of a mathematical process, whereas in the case of an X-ray image (e.g. an EPI) this is the result of a physical process - mainly due to attenuation of radiation in the body. In the latter case, image quality (contrast and geometric resolution) is deteriorated by the effects of scattered radiation and the finite size of the radiation focus. In addition, the attenuation coefficients of bone and soft tissue are closer for the high photon energies used in radiotherapy compared to the energies typical of diagnostic X-ray imaging. The resulting lack of recognizable fiducials means that image registration must be based on fragments of structures scattered over the image surface. The best match to these structures is not necessarily unique [92]. From the experience gained in the present work, and in the work of others, a human verification of the registration outcome is thus required.

The apparent added complexity caused by the collapsed BEV geometry may impede the intuitive interpretation of what is observed. Furthermore, the computer programs possess no a priori ability to make sense of the globally discernable patterns, and sophisticated pattern recognition methods may be needed.

5.2.1. Problems connected to alignment and registration in the BEV geometry

The correct alignment of a patient on the treatment couch constitutes a three-dimensional problem (or even a 4D problem) [93]. The comparison of portal with reference images in 2D sometimes yields insufficient information to establish a complete correction of the set-up in 3D [92]. Evidently, the BEV geometry of the EPI has shortcomings when it comes to the ability to assess out-of-plane rotations, i.e. rotations of the patient along axes that are not perpendicular to the image plane. Objects closer to the focus will, because of rotations, show a larger shift in the 2D image than objects close to the EPID, and may suffer from distortions due to the shifted perspective. In theory, this effect may be mitigated if the mutual distances are known, but this is rarely the case in clinical practice. Likewise, geometrical degeneracy in the alignment of rotationally symmetrical objects, like the femoral heads, often in combination with poor tissue contrast, may cause ambiguous 2D alignment from a single view (if possible such structures should not be used for image matching). As a consequence, analysis in 2D can only provides accurate measures of patient set-up deviations when such rotational errors are small. Studies have demonstrated that in the treatment of the prostate
cancer, out-of-plane rotations larger than 3 degrees of the pelvis may cause significant misinterpretation of the position of the isocentre inside the patient if interpretation is based on 2D images only [92].

5.3. The introduction of the in-treatment-room Cone-beam CT

The most striking technological accomplishment during the past decade is probably the advent of in-treatment-room volumetric kV-imaging. By applying a conventional X-ray tube and an EPID like flat panel imager mounted on the treatment gantry, 2D X-ray images can be acquired at a frame rate of typically 3-6 frames/sec as the gantry of the treatment unit rotates around the patient. A modified filtered back projection algorithm is then applied to reconstruct an image volume from these 2D images [20, 94-95]. The reconstructed images exhibit features comparable to that of conventional CT images: high spatial resolution (voxel size of 1x1x1 mm³) and good soft tissue contrast at low radiation doses. The CT like images have given rise to the acronym kV CBCT (kilovolt Cone-beam CT). The implementation of this technology has been instrumental in order to surmount some of the key problems of conventional MV based EPIs that may hamper image registration and degrade the effort of image guidance.

Cone-beam imaging has also been developed that utilizes the megavolt energy radiation and the standard EPIDs of the treatment unit (MV CBCT) [96-99]. However, the lower detector quantum efficiency as well as lower tissue contrast of the images produced, may pose some limitations on the clinical usefulness of this imaging technique compared to kV CBCT. On the other hand an advantage of the MV CBCT technique is the inherent reduction of image artefacts due to high Z materials such as dental fillings and prostheses. In addition, the images constitute a direct measure of how much the treatment beam is attenuated by the patient. As such the MV CBCT can readily be used for treatment planning and calculation and verification of dose without the need of a tabular conversion of the voxel values into a measure of electron density [100].

To get the most out the CBCT images, i.e. a quantification of the true set-up deviations in 3-D, methods to co-register the full CBCT data set and the planning CT have been developed. A mutual information criterion based on the grey values with no need for user defined templates, is frequently used. Alternatively, a 3D chamfer matching technique can be used where the extracted skeleton (or implanted fiducials for that matter) of the CBCT data is matched to the corresponding distance transform of the skeleton (fiducial) of the planning CT. The superior soft tissue contrast of the kV CBCT images has also made possible image
registration directly on tumour tissue. The latter has been reported for example for the
treatment of prostate cancer [101] and stereotactic radiotherapy of non-small cell lung cancers
[102]. These methods enable a very precise quantification of set-up deviations both wrt to
translations (Tx,Ty,Tz) and rotations (Rx, Ry, Rz).

Unfortunately, widespread access to satisfactory table top “mechanics” that facilitates
6D corrections of the patient pose is still scarce and is yet subject to clinical investigations. A
few “roll and tilt” tables have been put into clinical use, but a comprehensive corrective action
to account for the 6D set-up deviation vector is still in its infancy.

Non-rigid anatomy such as that found in the neck region, anatomy that easily moves
about such as extremities, or tumours located close to or even inside moving organs such lung
or liver tumours, can jeopardize the usefulness or correctness of the proposed 3D/6D
registration metric in CBCT applications. To alleviate this problem, vendors have introduced
clip boxes (one or many) or various types of image segmentation techniques that enables the
user to include in the registration, only the subsets of image data that are believed to be rigid
and of relevance to the treatment.

Recently, 4D CBCT imaging has also been made possible [103-104]. In this context
4D images relates to successive volume displays of the movements of the tumour and internal
organs as a function of time. Alternatively, techniques to estimate the respiratory motion have
been developed that subsequently have made it possible to correct for the motion effects
during the reconstruction of the 3D CBCT images (motion-compensated CBCT or MC
CBCT) [105-106]. These developments have aimed reducing the uncertainties and streak
artefacts induced by respiratory motion that can jeopardize the clinical usefulness of the
images.

In cases of non-rigid anatomy deformable registration algorithms, such as the “demons
algorithm” [107-108], have been implemented and tested to improve the 3D registration
accuracy. The key objective of this development is not to estimate set-up deviations to be used
for corrections, but more importantly to make possible a correct summation of dose delivered
on different sessions given the actual pose of the patient. This is an important prerequisite for
adaptive radiotherapy. Still, elastic (non-rigid) tissue (tumour) and patient body deformation
will continue to challenge the accuracy and precision of the treatment and is expected to be an
active area of research in the future.
5.3.1. Imaging in the Beams Eye View in combination with CBCT systems

Evidently, the 2D X-ray images created with the use of the X-ray tube of the kV CBCT system can play the role of the megavolt EPIs. A popular mode of operation is the acquisition of two orthogonal (or nearly so) X-ray images that are compared with DRRs created from the planning CT. This procedure has proven to be fast and straightforward, the superior tissue contrast inherent to X-ray images is maintained, and a large field of view can be used with negligible extra dose given to the patient. These factors all contribute to make the image registration fairly trivial. The stereoscopic (2D/3D) set-up verification can be performed by the use of either bony structures or implants as a fiducials, or by application of a mutual information criterion. By use of this technology automated and nearly real time registration seems achievable with satisfactory precision and consistency for a number of clinical scenarios. The technique has lately been extended to allow for tumour motion tracking during thoracic and abdominal radiotherapy [109].

Tumour motion during radiotherapy treatment delivery can substantially deteriorate the target dose distribution. The above mentioned technique has lately been extended to allow for tumour motion tracking during thoracic and abdominal radiotherapy [109]. The BEV perspective is used to identify the tumour position from projection images acquired during treatment and subsequent feed this information back into the MLC controller. At present, the tracking system latency, i.e. the time lag between the target motion and the correcting beam-target re-alignment, must be reduced in order for this concept to be clinically applicable. However, several groups have tested and demonstrated that it is feasible within seconds to reposition the MLCs according to the position of a tumour marker detected in a series of EPIs (Micropos). This development involves field edge detection in dynamic images and dedicated image segmentation methods to identify and describe the motion pattern of the tumour. The various BEV concepts studied and developed within the present NRH project can be extended to also handle tumour tracking.
6. Conclusion: Imaging and image processing in the Beams Eye View perspective

The work presented in the present dissertation has taken place in a clinical environment, and has benefited significantly from an enduring feedback from clinicians, medical physicists, and radiotherapy technicians. Such a process is unquestionably fundamentally different from an industrial development of software for radiotherapy. The latter would not be able to incorporate the many logistically complex interrelated activities that take place in the radiotherapy clinic. The scientific efforts were thus translated into thoroughly tested working modules that supported the logistically intricate interplay between systems and radiation therapy professionals. Evidently, some of the experiences gained by other groups were implemented in the IBV software, and some were developed in-house for specific purposes, most of which have been described in chapter 3.

The effort put into achieving high-quality external beam radiotherapy includes a large number of complex actions where each and every one is associated with a range of uncertainties. These uncertainties can be detrimental to the clinical efficacy of the dose that is deposited within the body of the patient during irradiation. Evidently the key notion of image guided radiotherapy is to minimize such uncertainties in order to optimize the treatment efficacy and thereby improve patient outcomes [110].

The present work has demonstrated the importance of the BEV concept for ensuring the geometric and dosimetric precision in external beam radiotherapy. The presented methods and processing techniques which have been implemented in the clinical setting have improved the quality of the treatment. This can be illustrated in the following ways:

At the time this project started in 1992 typically one or two portal films were exposed during each course of treatment and a visual inspection of the films on a light box was conducted. A visual judgement of the set-up accuracy was carried out keeping in mind that rather generous CTV-PTV margins – often of the order 1 cm - were used. The average number of treatment fields per target volume was slightly larger than 2 and CT based planning was used for around 20% of the patients. Digital imaging and imaging technology in the field of radiotherapy was literally in its infancy.

Since 1992 the complexity of a treatment plan has increased significantly. The average number of fields per target volume is now around 5 and for nearly 90% of the patients there exist a CT based treatment plan. Improved access to radiological imaging modalities in
treatment planning (i.e. more precise tumour delineation) has led to narrower treatment margins and in some cases made possible an escalation of the target doses. Obviously, the increased complexity and smaller margins entails a greater risk of both geometric and dosimetric misses. The presented work has been instrumental in gaining the required insight and awareness of the uncertainties that materialize in daily practice to counter-act any such potential increased risk. The new tools developed have enabled the staff to quantify and mitigate detected set-up errors systematically, efficiently, and with confidence.

Today the number of portal image acquisitions can be in the range 20 to 60 images during a treatment course – the latter number representative of daily imaging of head and neck patients treated with IMRT. Likewise, with the use of implanted markers in the prostate combined with daily orthogonal imaging (or kV CBCT), CTV-PTV margins as small as 2-5 mm have been feasible, and target doses of 78 Gy can safely be administered.

The systematic use of imaging and the knowledge gained thereof, was a prerequisite in assuring the treatment precision required when IMRT was implemented in the department more than 10 years ago for the treatment of head and neck cancers. Consequently an extensive off-line imaging protocol by the use of IBV was put into use to address the systematic errors that were regarded most important in such a highly fractionated type of treatment [111-112].

Recently the knowledge of and access to image guidance has been critical to the introduction of treatment options such as stereotactic radiosurgery of brain and lung lesions, as well as hypofractionated stereotactic radiotherapy of spine, lung and liver without the use of rigorous body frame fixation. For such treatments of large doses in a single or a few fractions, the random component of the set-up error is most important [63, 113] and an on-line image based set-up verification protocol is standard clinical practice.

The knowledge gained and tools developed for imaging in the BEV perspective in this project, has increased our confidence that the treatment is carried out according to the plan, i.e. that intended dose is delivered to the target, and has been vital to safe and sound introduction of new sophisticated treatment techniques. Nowadays the question is no longer “whether” imaging is needed, but rather “how much”.

6.1. Future prospects

For many years, radiotherapy strived at perfecting the treatment of the static, “dead patient”, improving the physical basis of the treatment, for instance through the development of photon based IMRT and intensity modulated proton therapy, to achieve outstanding geometric (and in 2011 arguably sufficient) dose conformity.
Clearly improved 4D characterisation of the tumour, anatomic and physically, and a capability to quickly redesign and adjust treatment plans from measurements of treatment response, are prerequisites in order to further enhance the efficacy of radiotherapy (i.e. cell kill for a given dose). This can only be accomplished by relating imaging and imaging technology intimately with the radiotherapy process. The minimum desirable irradiation dose (and possibly the maximum acceptable dose) may ultimately be prescribed from an image that describes tumour aggressiveness (dose painting by numbers). New technologies that facilitate such a development are currently being investigated or even being developed. Examples are combined MRI and PET modality that makes possible simultaneous measurements of anatomy and physiology [114]; integrated MRI and linear accelerators (MRIgRT) [115-117] that allow for millimetre precision in dose delivery guided by the superior soft tissue contrast of MR images, whole body PET/CT machines and real time tracking of tumour motion using fluoroscopy.

The next logical step into further improved treatment efficacy would be to examine and describe the dose distribution that results from treating an elastic, “live” patient and tumour, with these highly conformal techniques. Secondly, to account for any observed clinical response effects and adapt the remaining treatment accordingly. The synergy of recent efforts and advances in functional and molecular imaging and deployment of 3D/4D IGRT, may provide the means to move radiotherapy this step forward.

My view is that even after the introduction of multi-dimensional imaging, the BEV will continue to play an important role. In future developments the BEV may prove to be for the clinicians the most viable technique to provide an intuitive and instructive visualization of the complex multi-parametric information that enters radiotherapy planning and follow-up. The BEV constitutes an important tool for treatment planning and plan validation (DRRs) and for the verification of the treatment delivered (EPIs / PDIs). The BEV is as such an important instrument for ensuring as well as improving the treatment quality.
7. Bibliography


64. Eilertsen K. Development of standards for data exchange between imaging sciences and RT. *Radiotherapy and Oncology.* 2004 Oct;73:5196-S.


Paper I:

Eilertsen K and Skretting A
A novel algorithm for generation of DRRs enabling multimodality, limited range and maximum intensity projections.
Paper II:

Eilertsen K
Automatic detection of single MLC leaf positions with corrections for penumbral effects and portal imager doserate characteristics.
Paper III:
Sund T and Eilertsen K.
An algorithm for fast adaptive image binarization, with applications in radiotherapy imaging.
*IEEE Transactions on Medical Imaging* 2003 22(1) 22-8
Paper IV:

Sastre-Padro M, Lervåg C, Eilertsen K, Malinen E
The performance of Multileaf Collimators evaluated by the stripe test.
*Medical Dosimetry* 2008 34(3) 202-206
Paper V:


Paper VI:

Dahlgren C V, Eilertsen K, Dahl Jørgensen T and Ahnesjö A.
Portal dose image verification: The collapsed cone superposition method applied with different Electronic Portal Imaging Devices.
*Phys. Med. Biol.* 2006 51 335-349
Paper VII:

Arnesen MR, Eilertsen K, Malinen E.
Optimal treatment margins for Radiotherapy of prostate cancer based on interfraction imaging.
*Acta Oncol* 2008 *47* (7) 1373-1381
Eilertsen K, Nilsen L, Vestad TA, Geir O, Skretting A.
A simulation of MRI based dose calculations on the basis of radiotherapy planning CT. images.
*Acta Oncol* 2008 47 (7) 1294-1302