ESTRO WORKSHOP ON IMAGE-GUIDED RADIOTHERAPY

Saturday, September 24, 2005 – Lisbon

Rationale

1

Introduction to the workshop

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The last decade has shown a tremendous increase in the use of imaging techniques for the preparation and delivery of a radiotherapeutical treatment. For instance, the routine use of CT images for 3D target volume delineation and treatment planning was until recently only possible for a restricted group of patients because of the limited availability of CT scanners for radiotherapy purposes. Also the handling of various types of images by treatment planning systems has been improved enormously in order to fully exploit the increased knowledge of the 3D aspects of cancer treatment. The extremely fast development of imaging technology for diagnostic purposes in oncology has resulted in many applications for improved target volume delineation. CT scanners became much faster thus allowing imaging of movement of tumours and organs at risk, which should be taken into account both during treatment planning and treatment delivery. The use of MR imaging for target volume delineation has also considerably increased, including the exploration of its functional imaging possibilities. The latter option has also been implemented on a much larger scale in radiotherapy planning by the introduction of PET-based methods, combined in one or other way with CT information. Besides these developments in imaging for better target volume delineation, the use of imaging methods for treatment delivery verification has also been increased considerably by implementing techniques such as kV and MV cone-beam CT scanning just before, during or just after the actual patient treatment. Special equipment is now commercially available to employ these image-guided verification procedures in routine clinical practice. Besides the extensive use of images for external beam radiotherapy, image-guided brachytherapy is also now put into clinical practice at a much larger scale.

These developments have resulted in a number of changes in clinical practice in radiotherapy departments. In this workshop we will not only illuminate the technical details and possibilities of this new equipment, but also discuss the initial experience and clinical implementation of this new technology. Furthermore, the practical aspects related to the routine use of image-guided radiotherapy will be elucidated. The workshop will be finalized by a discussion on the possibilities and limitations of image-guided radiotherapy, in which various experts in the field will clarify different future scenarios.

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Possibilities and pitfalls of functional imaging

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The use of functional imaging in radiotherapy has becoming increasingly popular over the years…! Functional imaging can be used either as a predictive factor for tumor response, as an aid for treatment planning, or as a tool to evaluate modifications in organ function after treatment. The use of PET in general, and of FDG-PET in particular, for radiotherapy planning purposes has really taken a increasing importance up to a point that more and more radiation oncologists believe that adequate target volume selection and delineation cannot be performed adequately anymore without the use of FDG-PET! But what are the evidences supporting the use of FDG-PET in the treatment planning process?

Before answering these questions, one has to clearly understand the bottom line of the planning process, i.e. to select and delineate target volumes based on all the available diagnostic information and the knowledge of the physiology of the disease. The difficulty arises from the fact that not a single imaging modality does have a sensitivity and a specificity of 100% to depict neoplastic disease. If for a particular disease, the objective is to avoid by any mean the geographical miss of tumor cells, then the use of a highly sensitive modality -or highly sensitive criteria for interpretation- will be preferred. The price for that might well be that non-neoplastic tissue (called false positive) will be included in the target volume, but at least very few -if any-neoplastic cells will be left aside. On the contrary, if the objective is to avoid including non-neoplastic tissue in the target volume, then a highly specific modality -or highly specific criteria for interpretation- will be preferred. The price for that might well be that some neoplastic cells will not be included in the target volume (called false negative), but at least no undue normal tissue will be selected and delineated.

In that regard, when introducing a new imaging modality (e.g. FDG-PET), the question is thus really whether the new comer is more sensitive and/or specific than what one were used to use (e.g. CT), and consequently how could it modify the planning processes. For example, if an additional lymph node is visualized with a new imaging modality known to be more specific than the standard modality, it might be legitimate to enlarge -if necessary- the target volume(s) beyond what would have been done using a standard procedure to include this new node; conversely, if fewer nodes are visualized with a new imaging modality known to be more sensitive than the standard modality, it might be legitimate to decrease the target volume(s) below what would have been done using a standard procedure.

Another use of FDG-PET in the radiotherapy planning process is the delineation of the primary tumor GTV. For the primary tumor, the benefit of FDG-PET in the radiotherapy planning process should be evaluated more in term of 3D delineation and demarcation of the tumor volume from peri-tumoral inflammation, edema or atelectasis (for lung primary). In this respect, comprehensive studies have been already reported for lung, brain and head and neck tumors. Studies are ongoing for other locations such as esophageal and rectal tumors.

The lecture will concentrate on these various aspects of proper use of functional imaging with adequate clinical examples, and illustrate that the debate is not anymore "to PET or not to PET", but "when is it adequate to PET"…!

3

IGRT: What tools are available?

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Improper knowledge of the patient’s anatomy and position during the course of therapy has always been a major source of concern in radiation therapy potentially compromising the clinical results by insufficient dose coverage of the target volume and/or overdosage to normal tissues. The management of target localization emanates in the concept of treatment margins, such as those described in the ICRU reports 50 and 62. Image-guided radiation therapy (IGRT) aims at reducing these margins without compromising the clinical outcome. It is a category mistake in claiming that new techniques such as 3D conformal radiation therapy (CRT) and intensity modulated radiation therapy (IMRT) allow for reduction of the treatment margins. These margins (in particular PTV) should ideally reflect the geometrical uncertainty of the target localization and, consequently, CRT techniques allow realization of dose distributions that match the PTV. Moreover, as both the tumor position and the beam fluence pattern have a time dependence in IMRT, internal organ and tumor movement during treatment not only introduce an added risk of missing the target but also introduce errors in the dose delivery process due to a possible interplay. In this overview IGRT will be reviewed as a tool to detect and correct for patient set-up errors, patient movement, organ movement and organ changes. In fact with the introduction of the IGRT concept we move from patient oriented positioning towards target volume oriented positioning. The different IGRT techniques that have been introduced clinically at this date will be reviewed in function of: (a) solutions for reduction of the set-up margin (SM: to account for interfractional geometric uncertainties) only for those cases that present small or negligible intra-treatment organ movement; (b) IGRT solutions that aim for reduction of both SM and the internal margin (IM: to account for variations in size, shape and position of the CTV) for those cases that present important intrafractional organ movement. The choice of the technology to be introduced into a department largely depends on the patient flow, immobilization and treatment protocols. Clearly, the system requirements for single fraction or hypofractionated treatments will be entirely different from those for hyperfractionated treatment protocols. Finally, as CT-simulation has replaced conventional fluoroscopic simulation for 3D CRT and IMRT, image-guidance is not limited to the actual moment of treatment but needs to be properly incorporated/integrated at all steps in the treatment chain from imaging for treatment planning up to the actual treatment. Based on the IGRT approach that will be used, all imaging techniques should be adapted to cope with internal organ movement accordingly. Basically, the treatment procedure should be effective as well as efficient. This presentation aims at providing a comprehensive review of existing solutions in IGRT.

Imaging and treatment planning

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The use of "4D" imaging for Patient modeling

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The acquisition of temporally varying, or "4D", models of patients has been the subject of intense research and development over the past few years. While research groups are still struggling to discover methodologies for proper generation and use of these models, nascent commercial products are currently available, fueling discussion on the proper means to acquire data for and use information extracted from such modalities as 4D CT and PET. While assessing breathing-related movement is the dominant goal of must current systems, dynamic modeling can be used to manage physiological movement on arbitrary time scales (e.g. prostate movement), long-term changes in patient anatomy (tumor size and patient configuration changes over a treatment course), and physiological parameters (e.g., perfusion) related to treatment planning and assessment.

Formation of full patient models of breathing by current 4D imaging systems generally involves oversampling parts of the patient model, and subsequently sorting sampled information by the estimated phase of breathing in which they occurred. External sampling tools such as video systems and spirometers are the dominant means of labeling data by phase of breathing, although some small studies of internal tracking of movement for model building have been performed. 4D CT and 4D PET (by sorting decay events by breathing cycle phase) have been used primarily to aid in target (ITV) definition for treatment planning, although more advanced applications for direct dose calculation, as well as treatment setup verification, are under consideration.

4D models of long-term change are likely to play a future role in the emerging area of adaptive radiotherapy. In order to accommodate this information, a reliable and robust framework for deformable image registration, and subsequent use of deformable transformations for patient modeling and dose calculation/accumulation, is required. While initial versions of this infrastructure are under development at research groups, significant development will be needed prior to routine clinical use of this technology.

Finally, the concept of using dynamic models to select the level of complexity in treatment intervention for breathing is worth exploring. The need to use interventions such as gating or chasing may depend on patient-specific motion and treatment geometries. Surrogate position/movement information (e.g. implanted markers) may play a key role in this area, both validating observations from 4D patient models, as well as potentially providing inferred data of acceptable state for treatment with a temporal resolution far higher than 4D volumetric imaging and analysis systems have achieved to date.

This talk will focus on a number of areas related to patient modeling with 4D information. The major elements to discuss will be:

1. 4D imaging systems (CT, PET, MRI, fiducial tracking)
2. Building moving patient models
3. Using data from 4D models for treatment planning
4. Using data from 4D models for treatment verification

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4D CT/PET imaging: applications in 3DCRT planning and gated RT

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PET-based software for automatic delineation of the GTV

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Target volume delineation in external beam radiation therapy is an observer-dependent procedure. The assessment of tumour extension is based on the clinical data available at the time of treatment planning and is differently appreciated by individual oncologists. CT scans have a high spatial resolution, but a limited soft tissue contrast resolution. PET either alone or in combination with CT is increasingly used in target volume delineation. The addition of PET data to the planning procedure may reduce variations in target volume delineation and the time needed for treatment planning. However, a standardized way of converting PET signals into target volumes is not available at present.

Assuming a uniform signal emission from the tumour and surrounding normal tissues, a model-based method has been developed to determine a relative threshold level (Th_{rel}) for Gross Tumor Volume delineation. An analysis of measurements of cylindrical sources has shown that it is feasible to establish a target volume based on PET signals. A background-subtracted Th_{rel} can be calculated that best corresponds to the physical diameter of the sources. Software (SW) has been generated to automatically delineate volumes based on this Th_{rel}. Validation of the SW has been done by submitting images of spheres of ^{18}F activity for automatic segmentation of their volumes.

For the set-up used, it can be shown that a Th_{rel} of 35%±2.5% of the background-subtracted signal represents the source diameter. The Th_{rel} is constant for diameters ≥ 12.5mm. For source diameters < 12.5mm, the Th_{rel} of 35% over-estimates the real source diameter by a factor dependent on the physical diameter. In an in-vitro set-up the SW is capable of segmenting single PET volumes to within 1.4mm (1SD). It can thus be concluded that SW can automatically delineate the volume of ^{18}F activity. This has been shown to function accurately in an *in-vitro* environment, in conditions of uniform signals and that it can be integrated in the treatment planning process. The approach is highly reproducible and will speed up and increase the efficiency of treatment planning.

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MR-based simulation in radiotherapy: improving tumor definition, characterizing motion, and monitoring response

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The recent advent of dedicated MR scanners in the radiation oncology setting has advanced the integration of MR imaging into radiotherapy. The integration of MR-based simulation has the potential to improve tumor definition, characterize physiological motion, and provide the opportunity to monitor tumor and normal tissue response. The benefits of MR imaging for treatment planning have been shown for many sites including the brain, head and neck, breast, lung, liver, prostate, and cervix.

MR imaging offers outstanding soft tissue contrast for anatomical imaging, as well as the ability to perform functional imaging, for improved tumor identification and staging. MR imaging has also been shown to reduce inter-observer variations in tumor delineation. The integration of volumetric MR imaging into the treatment planning process requires multi-modality image registration, as CT remains the standard imaging modality for treatment planning. Although rigid registration is sufficient for treatment planning in some anatomical sites, such as the brain, many sites in the abdomen, thorax, and pelvis, require deformable image registration for accurate image fusion. The use of in-room lasers and MR-compatible immobilization devices allows the technologist to position the patient as close as possible to the treatment position, providing the initial global registration to CT.

Multiple imaging sessions and continuous, cine, imaging can be performed to determine a patient's inter- and intra-fractional motion, as no ionizing radiation is delivered. Monitoring of organ motion over a time scale of a treatment fraction can provide insight into the correct PTV margins for regions of interest that do not undergo periodic motion, such as the prostate, cervix, rectum, and bladder. Periodic motion due to breathing can be quantified using multi-plane cine imaging as well as taking advantage of parallel imaging techniques for faster imaging times, allowing volumetric imaging in a single breath hold.

The response of both disease and normal tissue can be assessed through the use of MR imaging, benefiting from the superior soft tissue contrast and the ability to image over several sessions without delivering ionizing radiation. Response monitoring throughout treatment can provide the information necessary for adaptive radiotherapy. Investigations are ongoing to determine potential for MR imaging to determine risk factors for normal tissue complications and identify them at earlier stages. The use of deformable image registration techniques allows the generation of response models and has the potential to improve normal tissue complication models, through the correlation of response with delivered dose.

CT-based imaging and delivery

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Kilovoltage cone beam CT guided radiotherapy

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To account for geometrical uncertainties and variations during radiotherapy, safety margins are routinely applied. In many cases, these safety margins overlap organs at risk thereby limiting dose escalation. The aim of image-guided radiotherapy is to improve the geometrical accuracy by imaging the tumor and critical structures on the treatment machine just prior to irradiation. The NKI has collaborated in the development of a kilovoltage cone beam CT guided linear accelerator. A prototype system has been in use for about 2 years, and two commercially released systems have just been taken into clinical use. The system extends the regular accelerator with an extra kV tube and aSi imager. Scan times (with concurrent reconstruction in the background) on the commercial system range from 35 s (small field of view, head and neck) to 120 s (large field of view, prostate). Preliminary results show that the image quality of the commercial system is similar to that of the prototype system, i.e., prostate localization is well possible with about 4 cGy imaging dose. For other anatomical locations less dose is required (we use 1 cGy for head and neck and 2 cGy for lung, 4D scanning). The availability of high quality tomographic images and automatic image analysis (registration) on the treatment machine has quickly led to the introduction of many new clinical applications in our institute. The most exciting ones are high precision hypofractionated treatments of brain metastases and solitary long tumors with on-line tumor position corrections. Patient localization with 1 mm accuracy (for bony anatomy) is easily achieved with the current equipment. Pre- and post-treatment scans demonstrate negligible patient motion (bony anatomy), i.e., about 0.5 mm SD, both for brain and bladder cancer patients. Another advanced application that is now in routine clinical use is adaptive radiotherapy (ART) of prostate cancer, where we determine and adapt the plan to the average prostate position based on cone beam scans made during the first week of treatment. The availability of cone beam CT on the linear accelerator makes this technique very efficient, since the patient does not need extra appointments for CT scans. It is also more accurate, since problem duplicating the setup of the treatment machine on the CT scanner do not occur. An important tool that we have implemented for these protocols is automatic registration of a selected region of soft tissue anatomy. This tool is used for automatic localization of the prostate, as well as for lung tumor setup based on 4D (respiration correlated) cone beam CT. However, for all image-guided protocols, the residual uncertainties need to be taken into account, and the safe level of margin reduction evaluated. For instance our prostate ART protocol allows a reduction of the margin from 10 to 7 mm. In conclusion, cone beam CT guided radiotherapy is now very much a clinical reality. The involved physicians and therapists are very enthusiastic.

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MV Conebeam CT; Performance and Clinical Applications

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In March 2005, a Megavoltage cone-beam CT (MV CBCT) system integrated on to a Siemens Primus linear accelerator was installed in the UCSF Comprehensive Cancer Center. To date, a total of 45 cone-beam CT images from 22 patients have been acquired using this system to provide 3D patient data in the treatment position. In this talk, we present the main advantages and performance of this MV CBCT system and summarize the different clinical applications.

The MV CBCT system consists of a new a-Si flat panel adapted for MV imaging and an integrated workflow application allowing the automatic acquisition of projection images, conebeam CT image reconstruction, CT to CBCT image registration and couch position adjustment. This provides a 3D patient anatomy volume in the actual treatment position, relative to the treatment isocenter, moments before the dose delivery, that can be tightly aligned to the planning CT, allowing verification and correction of the patient position. For a typical case, 200 projection portal images are acquired with the 6 MV beam in 45 seconds and the 256x256x256 MV CBCT image is reconstructed less than two minutes after the start of the acquisition. The image acquisition system performs very reliably. The dose used for MV CBCT depends on the clinical application but typically ranges from 2 to 8 cGy, the lower end being used when daily acquisitions are performed on a patient while 6 to 8 cGy are used for tumor evolution studies or for planning purpose.

Examples of the image-guided treatment process from the acquisition of the MV CBCT scan to the correction of the couch position and dose delivery will be presented for head and neck, lung and prostate anatomical sites. Other applications include the evaluation of tumor anatomical changes over time and the assessment of the resulting dosimetric impact using the density-calibrated MV CBCT image in a treatment planning system. The availability of a 3D imaging modality in the treatment room exposes to its full extent the problem due to the distortion of the anatomy occurring either between the CT and the treatment or between two different fractions. The application of MV CBCT for patients with tooth fillings, dental implants, implanted gold markers in the prostate or hip prosthesis will also be discussed.

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Linac with In-room CT: Technical Issues and Clinical Implementation

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A linear accelerator with in-room CT has been in clinical use at the Northern Centre for Cancer Treatment since December 2004. It has facilitated a number of quality improvement opportunities for both patient throughput and treatment delivery, and in the long term is intended to enable the use of proven rather than developing technology to be utilised for image guided radiotherapy.

The basic concept is a modern linear accelerator and in-room CT scanner; however consideration had to be given to the specification and design of the couch, lasers and software functionality. It was essential that the couch had mechanical and radiation properties appropriate for both imaging and treatment and rotated through 180° with a small tolerance. The rationale for the positioning of the lasers will be discussed. For optimum use the required functionality of the software was a virtual simulation application with direct input into the couch controls, this is not currently available and use of the current software application will be reviewed.

Particular installation and commissioning issues of the overall solution are discussed. The overall commissioning time did not exceed that of the individual components; however the alignment of the equipment took an additional three days.

Improvements in clinical workflow arising from changed working practices, facilitated by the equipment, have been implemented. For radical patients the tasks undertaken during pre-treatment verification and initial treatment appointments have been coalesced into one streamlined appointment. For palliative patients a single visit for both imaging and treatment has been achieved. Resolution of patient positioning problems has proved efficient using the in-room CT.

A series of imaging studies have been undertaken off-line, analysing the external marker position, bony landmarks and internal organ position for a number of sites.

- An analysis of setup problems for pelvis patients has resulted in increased immobilization for more tumour sites, including those not normally considered to require significant immobilisation.
- Analysis of bladder filling has indicated that the current instructions to patients are inadequate and a study is required to improve the consistency of bladder filling over the course of the treatment.
- A comparison of soft tissue and bony landmark matching is presented, which is possible without fiducial markers, and is a precursor to on-line image guided radiotherapy.

As a consequence of these analyses, improvements in the quality of the radiotherapy treatment have been achieved and as a first stage to on-line image guided radiotherapy, on-treatment imaging protocols have been modified.

In conclusion the perceived benefits of this equipment configuration and current limitations will be summarized and future developments at NCCT reviewed.

Image-guided brachytherapy

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3D CT-guided brachytherapy

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An overview on MRI-based treatment planning for brachytherapy of cervical cancer

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There is a clear trend that MRI-based treatment planning will play a major role in modern brachytherapy. Several centres in Europe started to integrate the use of MRI images for brachytherapy of gynaecological malignancies. The implementation process has to cover different clinical and technical aspects. The first step is to arrange a suitable infrastructure to perform the MR imaging. The most practical option is to have a MRI scanner close to the rooms for application and irradiation. Due to the invasive insertion it is important to reserve dedicated time slots for brachytherapy patients. Experience in different centres show the possibility to use a wide range of available devices including low field, open MRI scanners. For each device certain protocols including specific sequence parameters have to be defined to visualise targets, OARs and the applicators appropriately. Further technical requirements are a treatment planning system able to handle the images, a network connection and MRI compatible applicators.

Treatment planning is based on appropriate target and OAR delineation. The GYN GEC ESTRO working group published detailed recommendations on reproducible target volume definitions (Haie-Meder et al. 2005). As for target and organ structures the exact locations and orientations of the applicators and possible source positions have to be reconstructed with good precision. MRI images, for target and organs used with T2 weighting, have limited ability to show the exact applicator positions. One specific problem is the orientation of the ring, without any suitable MRI compatible dummy source wire available. To overcome such problems several procedures are currently applied in European centres, some of them already in daily clinical practice: image registration/fusion with orthogonal X-rays, CT or T1 weighted MRI and specific solutions using MRI markers.

The use of volume contours allows a target and OAR oriented treatment planning with individual loading patterns and dwell times. However, by now automatic dose shaping tools fail to produce appropriate dose distributions without changing the traditional loading pattern significantly. In the current situation, with experience in a limited amount of patients, manual adaptation starting with a standard loading seems to be appropriate. Each change has to be carefully monitored by a set of DVH parameters for the target volumes, rectum, bladder and sigmoid. Dwell time gradient and a high dose volume have to be considered in addition. The second part of the GYN GEC ESTRO recommendations (Pötter et al. 2005) introduces such a detailed parameter concept. It seems that the recommended DVH parameters are very close related to experience with point A and the 60 Gy reference volume. Traditionally used dose prescription and dose limits are transferable. Using image guided brachytherapy a pure intracavitary approach for large tumours or unfavourable topography results in only limited solutions for target coverage or organ sparing. Therefore this new treatment planning method is followed by new developments using interstitial needles. An overall approach consists of MRI guided applicator positioning and treatment planning based on a defined contouring and parameter concept.

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US-guided brachytherapy of prostate cancer

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Prostate brachytherapy dates from 1914 when Pasteau inserted retropubically radium needles into the prostate. In 1917, Barringer inserted transperineally radium needles into the prostate guided by a finger in the rectum. Young performed retropubic implantations of Radon seeds in 1922. Determination of prostate dimensions was very operator dependent and the quality of the insertion of the needles was low resulting in poor results of the treatment. The interest for prostate brachytherapy faded untill Whitmore et al. (1972) presented the retropubic implantation technique for I-125 seeds in 1972. Determination of prostate dimensions and insertion of the needles were still based on rectal palpation. A nomograph was used to determine the number of seeds and the spacing between them from the dimensions of the prostate in relation to the activity per seed. The developments of ultrasound caused that the prostate could be visualised and the prostate volume could be determined more accurately. It became possible to make a plan of the seeds distribution before insertion of the seeds, the so-called preplan. It was then realised that the uniform seed distributions resulted in high central doses and most centers moved to more peripheral loading patterns to get more homogeneous dose distributions to spare the urethra. It also opened ways for image-guided implant techniques. In 1983, Holm et al. described the technique for transperineal implantation of seeds for prostate cancer guided by transrectal ultrasonography. The needles were inserted into the prostate through a perineal template, which standardised the implantation technique. Improvements of the imaging technique and the introduction of computers into the operation room made it possible to plan the needles and the seeds distribution during the implantation, the so-called intra-operative planning.

Intra-operative planning consists of:
Intra-operative preplanning: creation of a plan in the operation room just before the implant procedure, with immediate execution of the plan.
Interactive planning: stepwise refinement of the treatment plan using computerized dose calculations derived from image-based feedback of needle position.
Dynamic dosimetry: constant updating of dose calculations of implanted sources using continuous feedback of deposited seed position.

Intra-operative planning has not yet reached the level of dynamic dosimetry due to poor visibility of I-125 seeds on US images and due to prostate deformations caused by needle insertion and retraction. Intra-operative dose calculation is thus based on updated needle positions rather than updated seed positions. Nevertheless, the mentioned improvements in implant techniques, imaging and intra-operative planning have resulted in more adequate dose distributions and better treatment results. The quality of prostate implants is measured by parameters like V_{100} (the percentage prostate volume that receives the prescription dose, usually 145 Gy) or D_{90} (the minimal dose in 90% of the prostate volume). In our own series of patients prostate coverage V_{100} has increased from 57±10% in 1994 to 92±7% in 2004. Recent developments are MRI-guided prostate implant techniques, which have the advantage of more accurate delineation of prostate anatomy and surrounding structures, but the disadvantage of limited space in MR scanners and the need for MR compatible devices. In Utrecht we started the development of an MR compatible needle implant device for prostate brachytherapy.

Clinical experience

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PET in radiotherapy planning and monitoring

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PET may be helpful in obtaining a clearer answer to three important questions:

1. Where is the tumor located and where are the (macroscopical) tumor margins?

The co-registration of PET with morphological imaging techniques seems to improve the delineation of viable tumor tissue compared to CT or MRI alone. Therefore, PET allows the definition of a target volume based on a biological paradigm (BTV) and increases in some cases our ability to differentiate between tumor and normal tissue as compared to CT and MRI alone. However, anatomical imaging will continue to be the basis of the treatment planning because of its higher anatomical resolution. Incorporation of PET into the tumor volume definition should only be done in tumors where studies clearly show increased sensitivity and specificity, based on histological evaluations.

2. What are the relevant biological properties of the tumor visualized by PET?

The imaging of hypoxia, angiogenesis, proliferation and apoptosis etc. leads to the identification of different areas of an inhomogeneous tumor mass that can be individually targeted. For example, hypoxic areas can be treated with higher radiation doses than non-hypoxic areas. This approach, closely related to the IMRT technique, has been named "dose painting". Thus, IMRT combined with a treatment plan based on biological imaging could be used for future biological individualization of radiation therapy. Clearly, the biological process visualized by the tracer needs to be specified. Therefore, the concept of BTV should be named after the respective tracer (i.e. $\text{BTV}_{(\text{FDG-PET})}$, $\text{BTV}_{(\text{FAZA-PET})}$).

3. What is the exact tumor response to therapy?

PET may be used to evaluate the response to different therapeutic interventions. Its value has been documented in several studies for patients treated with chemotherapy. Although evaluating the response after radiochemotherapy is often difficult due to treatment-induced inflammatory tissue changes, preliminary data in lung, esophageal and cervical cancer suggest that the decrease in FDG uptake after treatment correlates with histological tumor remission and longer survival.

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Impact of Observer Delineation Variation on Target Coverage and Dose to Organs at Risk in Nasopharyngeal Cancer Patients

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Purpose: To provide a qualitative and quantitative correlation between inter-observer variation and dose coverage of targets and organs at risk (OAR) in Nasopharynx Patients (NPC).

M&M: Ten nasopharyngeal patients' were included in this study. Ten Head & Neck radiation specialists delineated the Clinical target volumes (CTV) on CT with MRI and specific delineation instructions available. A median CTV was determined for each patient and accounted as the reference target volume. A 3D margin of 5 mm was applied to generate the planning target volume (PTV). The optical chiasm, brainstem, spinal cord and cerebellum were delineated for evaluation. The inverse planning module of ADAC Pinnacle$^{3\text{TM}}$ was used to generate an IMRT plan for each CTV, resulting in eleven different dose distributions per patient. The same constraints were applied for each treatment. An in-house software package (Uncert®) simulating random and systematic errors was used to calculate the dose to the median CTV and organs at risk (OAR) for each dose distribution, delineation and patient. The 95% and 90% dose volume to the median CTV was used to calculate the delineation effect on the CTV. The maximum dose was used to determine the impact of the inter-observer variation on dose to the OARs.

Results: a) The 95% dose coverage of the median CTV was 95.7% (SD 4.9). For the same volume, the 95% dose coverage dropped to 84.8% (SD 8.10) when the treatment plans designed for the individual observer PTVs ($p<0.05$). b) There was an impact of inter-observer variation on the maximum dose to the OARs. For the chiasm, brainstem, spinal cord and cerebellum, the percentage of patients unable to fulfill both the pre-set target and OAR dose levels due to difference in observer target volumes, was 50%, 70%, 10% and 70% respectively.

Conclusion: Inter-observer delineation variation has a quantifiable impact on target dose coverage and influences dose to the OAR's. Interobserver variation leads to underdosage, avoidance of designated tumor volumes and unnecessary radiation dose to normal tissues. Delineation variation has to be addressed and minimized for accurate and objective target delineation and ultimately for highly conformal radiation treatments.

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Image Guided Radiotherapy (IGRT) of Prostatic Cancer using the BeamCath Technique

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Radiotherapy treatment of prostate cancer have rapidly developed over the last ten years, moving from the large box-technique with a shrinking field, to the 4-field box technique using CT planning and further to conformal radiotherapy with shrinking margins and increasing doses. Publications in the mid 1990's suggested that dose escalation radiotherapy of prostate cancer could be of benefit. Later randomised studies (Pollack) showed that intermediate risk patients largely benefited, with increased relapse/PSA free survival and decreased metastasis at 5 years with modest dose escalation from 70 to 78 Gy in patients with PSA above 10. At ASTRO 2004 last year Zietman and co-workers showed that similar dose-escalation from 71 Gy to 79 Gy showed similar magnitude of benefit also in low risk patients. However, in these studies higher dose increased the risk of rectal toxicity. Previous author´s have shown that if the radiotherapy technique is not change, dose escalation radiotherapy of prostate increase the risk of rectal toxicity with 2-3 times. Therefore, over the last few years margins tend to decrease from 20-15 mm down to 5-10 mm around the prostate. However, studies have shown that to get full dose (95% of the dose) 10-15 mm margins are needed around the prostate. To overcome the risk of missing the tumour, new techniques have been developed to visualise the prostate position during radiotherapy treatment.

In Umeå we started in 1997 dose-escalation radiotherapy of prostate cancer using the BeamCath technique, a urethral catheter with fiducial markers. The technique has since 1997 been used in all prostate cancer patients at our department, and has now been used in more than 1500 patients in Scandinavia. Later different techniques have been developed, such as the BAT, the rectal balloon, the CT in the treatment rooms, CT on the gantry (CT-synergy). In later years implanted markers have also been used.

With these positioning techniques for the prostate we are entering the 4-D conformal era of radiotherapy treatment techniques for prostate cancer. We can now safer localise the prostate position during treatment, but which of these techniques that are most suited for the different treatments remains to be proven.

We are presently at the position in development of Prostate cancer radiotherapy were the errors in prostate treatment position in the treatment room are perhaps smaller than the errors when we define the target on the planning CT. To further improve our definition of the prostate target we need to use new forms of radiological supports predominantly establishing MRI as a standard support for prostate definition and delineation. Perhaps in the future also look at different forms of PET/CT techniques as well as MR-spectroscopy.

With shrinking margins using different forms of markers we have clearly showed that we can give dose escalation radiotherapy without any risk of increasing toxicity form radiotherapy. If the development of new HYPO-fractionations schedules are to be used a further decrease in margins are probably used and to make sure that the prostate get a full dose we really need to improve localisation, visualisation and definition of the target.

Initial experience

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MVCT - Guided Imaging

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Helical Tomotherapy is an innovative modality of delivering intensity modulated radiation therapy (IMRT) using a device that requires specific peculiarities of a linear accelerator and an helical computed tomography (CT) scanner.

The same radiation source, used for treatment, can be used to generate megavoltage CT (MV_CT) tomographyc images. The possibility to acquire MVCT images offers verification of patient position prior and during radiation therapy, providing more anatomical details than the conventional radiotherapy "port films" used for set-up verification. In addition, MVCT imaging may potentially enable the reconstruction and therefore the verification of the effective radiation dose delivered in the patient during treatment, in order to compare the dose distribution actually delivered with the planned one and to eventually adjust the daily delivery to obtain the intended dose distribution (Adaptive Radiotherapy).

A mutual information registration algorithm allows the automatic alignment between MVCT and planning images. Lateral, vertical and longitudinal couch shifts are automatically estimated to match KV- and MV-CT images; rotational deviations can be corrected by changing the treatment irradiation starting angle.

The initial experience at San Raffaele Hospital of daily use of MVCT to correct set-up patient prior to treatment will be reported for different anatomical regions: systematic and random set-up error will be estimated by using on-line as well as off-line set-up correction protocols.

An example of the daily use of MVCT for post-operative prostate cancer (Hypofractionation schedule 20 Gy; 2.9 Gy/fr) to model the average systematic error and the residual error and to assess the minimum number of treatment sessions necessary to correctly estimate systematic set-up error will be reported.

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Image guided radiosurgery of moving targets by means of the Cyberknife system: principles, estimation of accuracy and precision, pitfalls and proposed solutions

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The Cyberknife system is a robotic, linac-based device for image guided radiosurgery. Image guidance is provided by the comparison of digitally reconstructed radiographs (DRR) to actual x-ray images of the skull (intracranial lesions) or of a set of fiducial gold markers (extracranial treatments).

A subsystem of the Cyberknife, called Synchrony, allows dynamic radiosurgery to be performed. The system is based on the correlation between the position of external, optical markers to the position of the internal gold markers.

The good conformity achievable with the Cyberknife and its inverse planning strategy could in principle allow radical treatment to be performed even in "difficult" or previously irradiated anatomical regions. Spatial accuracy in extracranial radiosurgery is however affected by organ motion. Static techniques require to enlarge the planning target volume (PTV) in order to guarantee tumour coverage; nevertheless PTV enlargement implies irradiation of bigger volumes of organs at risk (OAR). Two possible solutions exist: 1) gated techniques, which allow smaller volumes to be irradiated but negatively affect treatment times; 2) dynamic strategies as the Synchrony system, with which the irradiated volume can be kept reasonably small while preserving treatment times.

In a study aimed at characterizing dose sparing capabilities of the Synchrony system, we estimated PTV volume reductions of 38% (average) for liver lesions, 44% (average) for lung targets and 8.5% (average) for pancreas treatments. Volumes of 50% isodose surfaces undergo similar percentage reduction. This reduction implies NTCP reduction, whose magnitude depends on the type of OAR. For example, NTCP of the healthy lung surrounding the target was reduced from 2.5% to 0.1% in the case that presented the higher NTCP. For liver cases, NTCP varied from 23.1% to 14.5% (average). Differences in NTCP for the pancreas cases were negligible.

Accuracy and precision of the Cyberknife system was assessed by means of an "end-to-end" test, aimed at simulating the whole process including CT scanning, treatment planning, image guidance, linac and robot performance. A head phantom was used with a couple of perpendicular radiochromic films inserted in a removable plastic cube. A treatment plan was prepared in order to achieve spherical dose distribution for the 70% isodose surface. The centroid of the dose distribution was then compared to the expected position.

Results on 15 tests showed average displacement of 0.4 ± 0.8 mm (2□).

Accuracy of the Synchrony system was also studied by amplitude, frequency and baseline modulation in order to test the capability of the system to track variable breathing patterns. A motorized phantom was used to simulate respiratory motion, modelled after a study published by Shirato et al on 21 patients with lung cancer. The position of a narrow laser beam indicating the x-ray beam axis was recorded and compared to the expected position on a point fixed to the external surface of the phantom.

The results showed that amplitude and frequency modulation are easily corrected for by the system, while baseline modulation causes a systematic offset to be introduced.

By using Synchrony one shall be very careful in situations where the set of fiducial markers used to identify the target could move towards OARs more than expected by taking into account the single CT examination used for planning. Typical examples from the clinical experience are the proximity of lung targets to the spinal cord and/or to the oesophagus, and the location of pancreas targets adjacent to the duodenum.

A first but non complete solution to this problem can be the use of multiple imaging modalities. Use of MR datasets fused to CT allows the spinal cord to be distinguished from the larger spinal canal, thus providing information on the safety margin attained by using the spinal canal as a limiting structure. An intermediate solution is offered by taking CT volumes in the two extreme phases of the respiratory cycle. Only one scan will be used for treatment planning, but the isodose distribution can be calculated also on the other phase (referred to the new position of the set of fiducials), thus providing the full range of variation if a linear model is assumed for the displacement. The most accurate solution would be exploitation of a full 4D CT dataset, i.e. a set of time-dependent CT volumes describing one complete respiratory cycle.

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Gated radiotherapy - initial experience

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Gated radiotherapy is most often understood as a method of irradiating a target that moves with respiration in only a pre-specified phase of the breathing cycle. By reducing the movements of the target, it may be possible to reduce the margins necessary to take geometrical uncertainties, including respiratory motion, into account, and hereby reduce the amount of healthy tissue irradiated and hence reduce side effects. A prerequisite for such a margin reduction is however that the respiratory pattern is stable and the level reproducible between successive fractions during the complete course of treatment. Even if margin reduction may be hard to achieve, gating can be useful to geometrically separate the target tissue from organs at risk, as in the case of gated breast irradiation where the heart can be kept outside the treatment fields when irradiation is gated for inspiration.

How to gate and what problems may be encountered is, among other things, highly dependent on the site of treatment:

1) For the treatment of breast cancer, which was the first site to be investigated at Rigshospitalet, the first step of clinical introduction was to investigate different breathing manoeuvres, e.g. deep inspiration breath hold, end expiration free breathing and end inspiration free breathing and compare the dose distribution obtainable. As a result it was decided to treat all left sided breast cancer patients referred to adjuvant irradiation of the breast and the internal mammary nodes with audio coached, end inspiration, free-breathing gated beams. So far 59 patients have been treated in this way.
2) For the treatment of lung cancer, other aspects than for breast treatments must be addressed. As an example, the significantly lowered density of the lung tissue for end inspiration gating or deep inspiration breath hold, makes the modelling of electron transport in the TPS a crucial issue. Furthermore, the pattern of target movement and its stability with time over the whole course of treatment must be monitored and may add significant complexity to the treatment. The breathing capacity is often limited for these patients and different kinds of coaching may be necessary.

There are still many questions to be answered regarding gating. It is still unclear in many situations if, or how much margins can be reduced. Different approaches of coaching seem to be one way to improve the reproducibility of breathing. Another important aspect of gating is how it interacts with IMRT. Is IMRT competing with gating or is gating in some cases a prerequisite to do IMRT?

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MRI-guided IMRT of tumours of the cervix

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The conventional treatment of advanced cervical cancer consists of a combination of chemotherapy and radiotherapy. External irradiation is used to treat the primary tumor, the draining lymph nodes and a volume suspected of microscopic disease.

While conformal techniques and IMRT are used for the treatment of many types of cancer, their use for cervical carcinoma is complicated for several reasons. The target volume for external irradiation is complex and consists of the primary tumor, positive lymph nodes and multiple structures suspected of microscopic disease. Daily variation in bladder and rectum filling causes variations in relative position and orientation of these structures. In addition, fast tumor regression may occur during the course of the treatment, resulting in loss of conformality of irradiation.

We routinely use MRI for IMRT treatment planning. In weekly MRI scans during the treatment the internal motion of the CTV and the volume of the primary tumor is assessed. If sufficient regression has occurred (> 50 cc reduction) a new IMRT plan is generated.

Brachytherapy is used to boost the dose to the primary tumor (to approximately 80 Gy in point A). MRI scans are made with the Fletcher applicator in place to facilitate brachy planning. We found that the coverage of the tumor correlated inversely with tumor size. In particular tumors that were large (over 40 cc) at the time of brachytherapy could not be irradiated adequately. As alternative we studied the use of IMRT for integrating the boost into the external treatment. While such an approach could be beneficial, its benefit over brachytherapy vanishes when realistic PTV margins are included. Only for large tumors IMRT may improve the dose coverage even for margins of 15 mm.

We approach this problem along three lines. First we work on modifying the standard application so as to improve coverage of larger tumors.

Secondly, we use dynamic contrast-enhanced MRI to measure blood perfusion before and after one week of treatment so as to assess response to treatment. This may allow an individual treatment set-up where patients with large tumors that regress slowly receive an IMRT boost, and the other patients brachytherapy. However, the optimal solution will be on-line MR image guidance to reduce PTV margins. For such an approach an integrated MRI-accelerator is essential.

Clinical implementation

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Image guided radiotherapy: clinical and practical experience using X-ray volumetric imaging

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Since the introduction of X-Ray Volumetric Imaging (XVI) at the Christie hospital in 2003 we have undertaken a systematic investigation into the utility and potential benefits of XVI. This investigation has evaluated all anatomical sites culminating in the practical development of research studies and clinical protocols. XVI has demonstrated itself to be functional and unique due to its superior visualisation in 3D of bony anatomy and soft tissue and the ability to assess planning target volume (PTV) and organs at risk (OAR). The improvement to treatment delivery and technique accuracy has been promoted with the introduction of clinical imaging protocols at two anatomical sites. Firstly in the prostate to monitor organ motion and facilitate safe dose escalation, secondly in the brain for potential margin reduction due to proximity of organs at risk.

This presentation will examine the research and clinical focus of the work undertaken at this institution, ranging from audit of systematic & random errors, monitoring and evaluation of complex internal organ motion and a comprehensive assessment of imaging dose. The practical implications of image guided radiotherapy in view of increased treatment times, change in practice, training issues and the translation of this work from a research environment to a clinical department will also be discussed.

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Cone-beam CT experience in Aarau

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Purpose: For image-guided radiotherapy (IGRT) the different vendors of linear accelerators offer new kV imaging tools. These systems include - besides a radiographic and fluoroscopic mode – CT functionality. In August 2004 the second Varian On-Board Imager™ (OBI) has been installed at our Institute. After implementation of radiographic and fluoroscopic mode in clinical routine, a beta version of cone-beam CT was installed for clinical evaluation in October 2004. The aim of this study was to determine image quality in comparison with data from diagnostic CT scanners and to evaluate the future potential of a cone beam CT option for patient repositioning as well as therapy planning purposes.

Materials and Methods: The Varian OBI cone-beam-CT option consists of a kV-source and a kV-Imager mounted on robotic arms perpendicular to the MV therapy beam. In a single 360° rotation a volumetric CT data set of 17cm length can be acquired by collecting fluoroscopic images with up to 900 projections. Two different modalities with either full or half fan setup offer a 26.6 or 48 cm field-of-view, both with a physical aperture of 88 cm. In order to widen the dynamic range and to prevent saturation of the imager so called bowtie-filters are used to modify the beam profile.

Results: Comparisons of data between a diagnostic CT scanner and the cone-beam-CT (CBCT) with regard to topography and Hounsfield unit representation for a humanoid phantom indicate good accordance, the latter within 5%. Low contrast resolution in CBCT slices turns out to be even better than for diagnostic CT scans, i.e. for 0.5% contrast difference an object with 4mm diameter can be detected. The spatial resolution of CBCT data is inferior to a diagnostic CT scan; maximum line pair number per cm is 2 for half fan and 4 for full fan setup. Central axis doses applied during acquisition of one volumetric data set are between 3 and 8 cGy. Preliminary treatment planning studies using CBCT data with a standard Hounsfield unit calibration already give good results, i.e. monitor units compared to planning based on diagnostic CT data are within 2% and the relative dose distributions are nearly identical.

Conclusion: The CBCT option is in clinical evaluation now for about one year; during this period approx. 50 patients have undergone CT scans under treatment conditions. Our experiences show that the OBI cone beam CT option allows a real 3D setup verification followed by a 3D matching which takes also soft tissue information into account. Cone beam CT also is suitable to serve as a control CT for monitoring during the therapy period. As the acquisition time for the scan is around 1 minute, blurring due to organ motion is a limitation. Therefore gating as next step will be implemented for the acquisition of 4D-CT scans. Furthermore the planning studies indicate that CBCT data could probably in the future be used for planning and even allow - in a later stage - online re-planning. In order to improve the accuracy of dose calculation and scan field homogeneity a more sophisticated electron density calibration and an improved scatter correction algorithm are currently under development.

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Treatment verification: the use of markers and EPID's

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Introduction: Precise imaging and targeting for radiotherapy allows dose escalation while avoiding toxicity of the surrounding normal tissues. The aim of imaging for treatment verification is to evaluate the geometric uncertainties both due to organ motion and setup variations.

Portal imaging using bony structures can only detect set-up variations. If implanted markers are used as fiducials, both set-up variations and internal organ motion can be detected and –if necessary- corrected. Two types of deviations have to be distinguished: the day-to-day (random) variations and the systematic variations, present during all treatment fractions. Both the set-up variations and the organ motion have random and systematic components.

The use of gold markers for positioning verification has been reported mainly for the irradiation of the prostate; investigations have started for head-and-neck, lung and liver.

Method and Results: In prostate radiotherapy, the actual position of the prostate can be visualised and verified by using gold markers.

In Nijmegen, so far, fiducial gold markers were implanted in prostate patients (N= 250) who received external radiation therapy with either 3D conformal radiotherapy (CRT) or intensity modulated radiotherapy (IMRT) for treatment. Four fine gold markers (1 x 7 mm) were inserted in the prostate under trans-rectal ultrasound guidance by an urologist.

To verify the treatment position of the prostate, portal images were acquired with an electronic portal imaging device (EPID), using the first 30 monitor units of the orthogonal treatment beams. To analyze patient and prostate position variations, the marker contours derived from the DRR, were displayed overlaying the portal image and manually matched.

The random error in the prostate position, derived from the gold markers, is defined as the SD of the day-to-day variations, averaged over all patients in the group. The systematic error is defined as the SD of the distribution of average prostate deviations per patient.

For inter-fraction prostate position corrections, the so-called No Action Level (NAL) off-line protocol can be used. With this protocol the systematic errors can be reduced, with a minimum of extra workload and hardly any extra treatment time necessary on the accelerators. The deviations were measured and corrected after the third treatment fraction.

To correct both systematic and random errors, an on-line correction procedure is applied. After manual alignment of the marker template onto the portal image, the set-up deviations and required corrections are displayed. Set-up deviations in ventro-dorsal directions are corrected and checked again, before the irradiation dose is administered. This protocol is combined with a NAL correction protocol for the left-right and cranio-caudal direction.

Overall, the measured migration of the prostate markers was less than 1 mm and hence considered to be negligible. The systematic deviations ranged from 1.2-1.4 mm and the random deviations ranged from 2.0-3.2 mm, calculated after applying a NAL correction procedure. These results are comparable with those from other studies (table 1).

Prostate position relative to isocenter	Systematic deviation (x,y,z; 1 SD, mm)	Random deviation (x,y,z; 1 SD, mm)	Mean of means (x,y,z; mm)
Nederveen (N=23)	0.6, 0.6, 0.9	2.4, 4.0 3.0	-0.3, -0.1, -0.1
de Boer (N= 15)	1.0, 1.3, 1.5	1.7, 2.1, 2.5	-0.2, -0.6, -0.3
Van Lin (N=137)	1.2, 1.2, 1.4	2.4, 2.0, 3.2	0.0, 0.8, -1.0

Table 1: results after applying an off-line correction procedure on prostate markers

The first result from the applied <u>on-line</u> correction (N=12) procedure (only for ventro-dorsal direction) showed a systematic error of 0.4 mm and an average random error of 0.9 mm.

Conclusion and Discussion: Implanted fiducial markers allow detection and correction of organ and/or tumour-specific position variations. Most experience has been obtained in high-dose, high-precision prostate treatments, but fiducial markers have shown to be useful in other anatomical sites, such as head and neck, lung and liver. Depending on accuracy requirements, off-line correction protocols appear to be effective in reducing systematic deviations at an acceptable workload. With on-line corrections a very high geometric accuracy (< 1mm) can be obtained, but at the cost of a considerably larger effort.

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Clinical Implementation of IGRT Techniques

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Improved geometric accuracy through image guided therapy in radiation treatment delivery can reduce the volume of normal tissue irradiated. This may lead to a possible escalation of dose. We have been analyzing methods to quantitatively assess the geometric gains from IGRT. One application of IGRT at MGH involves improving partial breast irradiation setup. A three dimensional video surface imaging method is used to bring the treatment day breast surface into alignment with a reference surface. This method assumes a high degree of correlation between the breast surface and subsurface target location. Surface matching alignment is critically compared with other methods such as conventional laser based setup or alignment of chest wall from orthogonal radiographs. Using radio-opaque clips around the seroma as ground truth, we apply target registration error (TRE) analysis to quantify the relative accuracy of the different methods. Preliminary analysis shows a TRE of ~ 6-8mm for laser or chest wall based alignment vs. 2-3 mm TRE for surface matching. A statistical analysis shows the differences are meaningful.

In the second approach to IGRT, we describe an image guided / gated treatment method for moving organs such as liver tumors. Patients are 4D CT scanned and target motion is quantified. Gated treatment is indicated when large excursions are observed under normal breathing, in order to reduce normal tissue irradiation. In the case study presented, gating reduces tumor motion from 2 cm to ~5mm using a 30% respiratory window. This reduction in target motion permits the use of smaller apertures, which in turn reduce dose to normal tissues. The gain in IGRT is realized by acquiring gated setup images on a daily basis to ensure appropriate field placement. Gated treatment is then typically delivered at exhale respiration phase. An approach to validate accurate delivery of gated treatment has been developed.

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