

---

# Image Guided Radiation Therapy

Calvin Huntzinger  
Varian Medical Systems  
Palo Alto, California

Volumetric imaging and planning for 3-D conformal RT and IMRT have pressured the oncology community to better understand the geometric uncertainties inherent in the RT delivery process, including set-up error (inter-fraction) as well as organ motion during treatment (intra-fraction). This has ushered in the development of emerging technologies and clinical processes collectively referred to as Image Guided Radiation Therapy (IGRT). The goal of IGRT is to provide the tools needed to manage both inter- and intra-fraction motion to improve the accuracy of treatment delivery. Like IMRT, IGRT is a process involving all steps in the treatment process including patient immobilization, CT simulation, treatment planning, plan verification, patient setup verification & correction, delivery, and QA.

The technology and capability of such a system developed by Varian Medical Systems (Palo Alto, California, USA) is presented. The core of this is a Varian Clinac® equipped with a gantry mounted imaging system known as the On-Board Imager™. This includes a kV X-ray source, an amorphous-Si based kV image detector and 2 robotic arms that independently position the kV source and imager orthogonal to the treatment beam. A similar robotic arm positions a MV portal imager allowing both to be used in concert. The system is designed to support a variety of imaging modalities. The following applications and how they fit in the overall clinical process is described: kV and MV planar radiographic imaging for patient repositioning, kV planar fluoroscopic imaging for gating and tracking, and kV volumetric cone beam CT imaging for patient repositioning

**Keywords:** IMRT, IGRT, CBCT, Image Guided, Cone Beam

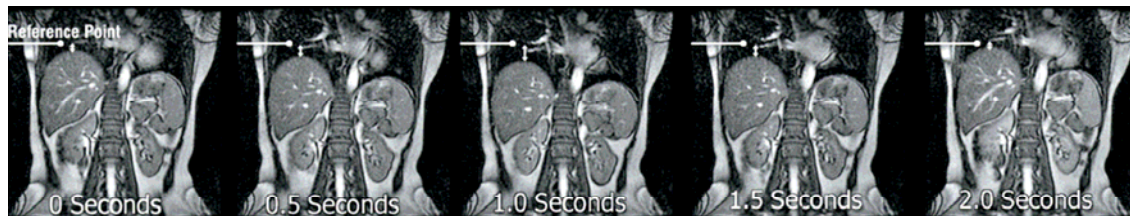
## INTRODUCTION

Radiotherapy is one of the most effective modalities for the majority of cancers and, with surgery, remains the most cost-effective way of curing many cancers [1]. Technical, academic and clinical advances in radiotherapy have improved patient management and outcomes significantly. The development of more sophisticated approaches to radiotherapy treatment have been made possible by improvements in radiographic imaging techniques such as magnetic resonance (MR), computed tomography (CT), by 3-dimensional and “inverse” treatment planning, better patient positioning, and more sophisticated linear accelerator technology. Radiation fields can now be shaped by means of computerized planning, automated tracking techniques and intensity modulated radiotherapy (IMRT) including the use of multi-leaf collimators with up to 120 leaves for high resolution IMRT. Considerable research has also been performed in defining the most appropriate fractionation schedules [2] with developments such as continuous hyper-fractionated accelerated radiotherapy (CHART) [3].

A review by Read [4] describes clinical trials that demonstrate the benefits of conformal techniques. These have mostly been done in prostate cancer but it the technology also has similar benefits in other cancers including Head & Neck. The rationale is that by conforming the target volume more accurately to the shape of the tumor, the consequent reduction in the volume irradiated will allow escalation of the radiation dose and hence an improvement in local control. Furthermore diminishing the irradiation of adjacent normal tissues will reduce morbidity and toxicity. Conformal radiotherapy offers the greatest advantage at sites where existing local control is limited by the collateral dose to normal structures. The introduction of IMRT

has further improved outcomes by increasing organ sparing, providing better local control of disease, enhancing quality of life and reducing treatment associated morbidity. [5] [6]

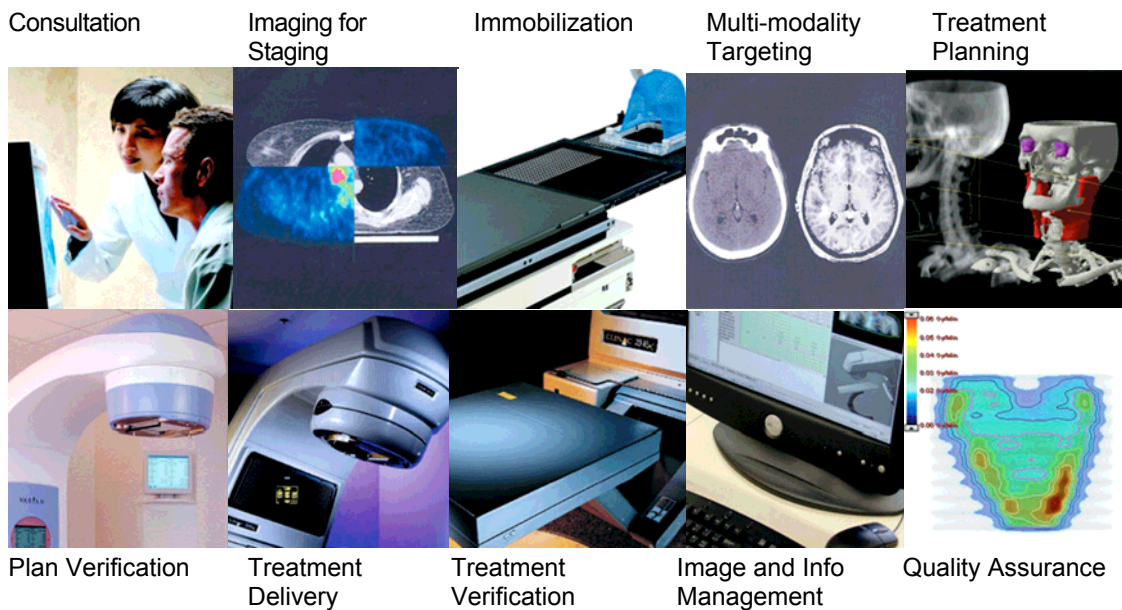
A fundamental tenet of radiation therapy is that successful outcomes require accurate alignment of the treatment beam to the target volume [7] [8] [9]. Reducing the field margin without compromising radiation dose to the CTV is particularly important in the proximity of organs at risk. However, tumors can move throughout a treatment regimen. Tumors are also subject to inter-fraction motion; changes in position from day-to-day. Factors leading to setup uncertainties include the therapist's skill in setting up the patient, variable filling of digestive or urinary organs, weight gain or loss or even the patient's cognitive state. In addition, tumors experience intra-fraction motion; changes in position during a treatment session. The main contributors are normal respiratory, cardiac and peristaltic organ motion along with voluntary movement. If the daily setup error including intra-fraction motion is greater than the treatment-planning margin, the prescription dose to the target may not be achieved or the tolerance dose to the normal tissues may be exceeded [10] [11] [12] [13].



**Image 1:** This sequence of MRI images shows the extent to which a reference point on the lung moves over a two-second period due to respiratory motion (intra-fraction motion).

**Image-guided Motion Management in the Radiation Therapy Process**

Varian Medical Systems (Palo Alto, California, USA) has introduced Dynamic Targeting IGRT™ a set of tools for image-guided radiation therapy to provide means for effectively handling inter- and intra-fraction motion. The Dynamic Targeting approach, pioneered by Varian, provides a suite of tools that work together to achieve better target localization across the clinical radiation therapy process. Dynamic Targeting focuses on localizing and managing motion based on internal anatomy, not just on the conventional external marks or tattoos.

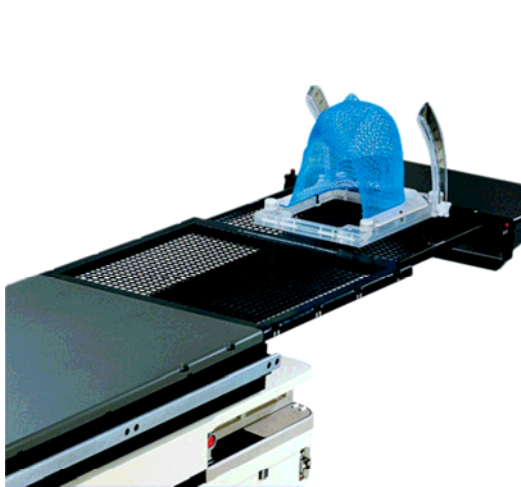


**Image 2:** The radiation therapy process, from imaging and planning to treatment delivery and verification.

The steps of a typical clinical radiation therapy process include: imaging for staging, immobilization, imaging for planning, treatment planning, post-planning verification, treatment delivery, imaging for treatment verification, image and information management, and quality assurance. Effective strategies for image-guided motion management affect all of these stages. Varian's suite of Dynamic Targeting tools—including the Exact™ Couch with Indexed Immobilization™, the RPM™ Respiratory Gating System, the Acuity™ simulation system, the PortalVision™ electronic portal imaging system, and the new On-Board Imager are designed to incorporate motion management into the clinical process.

### **Immobilization: Physical and Electronic Methods**

For accurate imaging and successful management of inter- and intra-fraction motion, patients need to be consistently positioned. Variation in patient position can be minimized with the help of precise patient positioning systems and rigid immobilization devices. Patients can be immobilized on a couch, such as the Varian Exact Couch with Indexed Immobilization, in the same position during all imaging, simulation, and treatment sessions. Otherwise, systematic errors can be introduced, resulting in larger margins [14].



**Image 3:** Exact™ Couch with Indexed Immobilization™

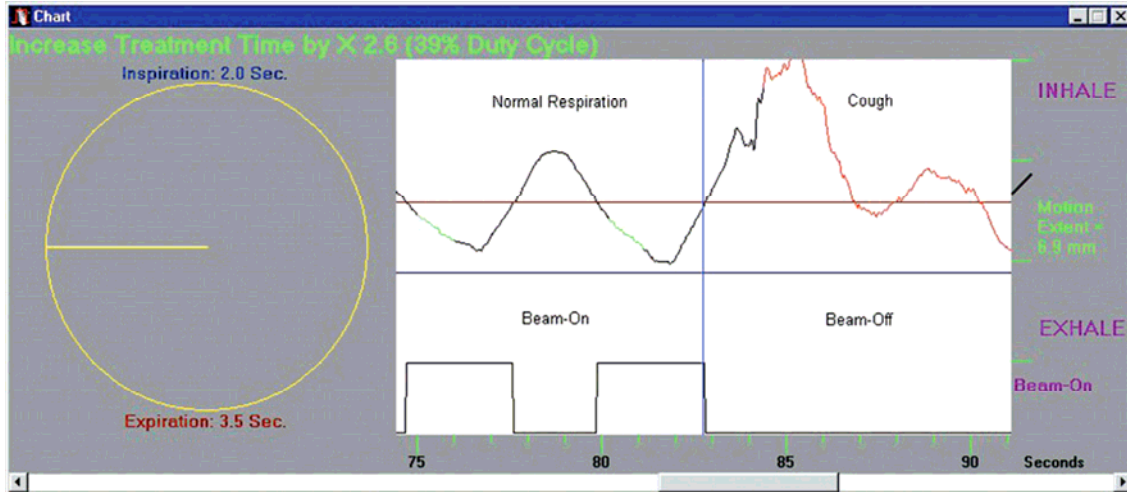


**Figure 4:** Passive infrared-reflective marker block used to track chest wall motion.

Management of tumor motion due to respiration has been achieved with both physical and electronic methods. These include: voluntary breath hold [15], deep inspiration breath hold (DIBH), [16] [17] Active Breath Control (ABC), [18] and physical restraint [19]. These methods offer the advantage of being relatively simple to implement. However, they suffer from the disadvantage of limited patient compliance because they require momentary cessation or constraint of breathing by patients who typically already have limited respiratory capacity.

An alternative technique is called “gating,” an electronic method of limiting the effect of normal, intra-fraction motion. Gating enables a radiation beam to selectively treat a moving target by electronically turning the beam on and off at specified intervals—effectively “freezing” the tumor in position, [21] [22] [23] [24] much like a strobe light can appear to freeze a moving object. For example, the RPM Respiratory Gating System uses an infrared camera to track a passive marker block placed on the patient's chest or abdomen. The system then processes the tracked motion to characterize the patient's normal breathing pattern in the form of a respiratory waveform.

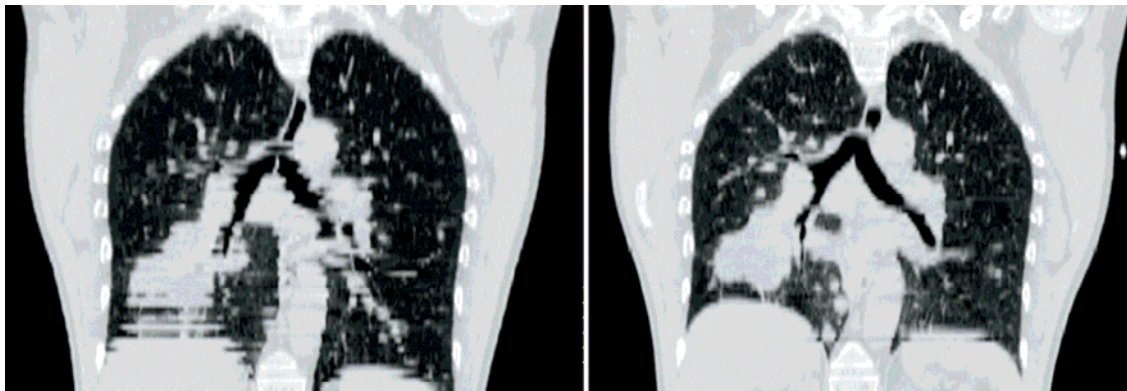
The data is typically gathered during computed tomography (CT) simulation so that the respiratory motion can be synchronized with the CT image acquisition. The resulting CT images can then be used to create a treatment plan that delivers doses at the desired point in the respiratory cycle. During treatment, the system automatically gates the radiation beam on only when the tumor falls within the planned treatment field. Abnormal motion that deviates from the regular respiratory cycle is automatically filtered out. Throughout the simulation and treatment processes, the patient can breathe naturally and remain comfortable.



**Figure 5:** The RPM Respiratory Gating software is used during simulation to optimize the beam-on interval, for treatment delivery with beam gating based on the patients breathing pattern.

**Imaging and Treatment Planning: The Advantages of Gated 4D CT**

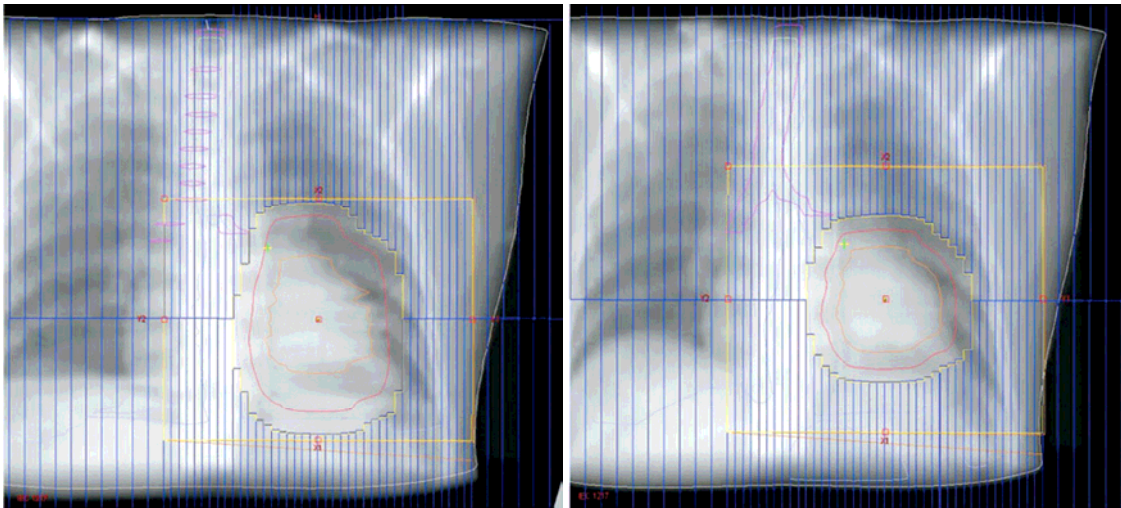
Tumors and organs can move up to 3 cm with respiration, so CT data for planning must target the tumor position at would be during treatment. Traditional CT images show respiratory motion as artifacts. Consequently, target volumes based on these images may end up being distorted and larger than necessary. To account for and to visualize tumor motion, information is needed from a fourth dimension—time. The capabilities of 3D CT are extended through four-dimensional (4D) CT technology, which allows clinicians to view volumetric CT images changing over time. The acquisition of 4D-CT data can be synchronized with a respiratory phase signal, such as that provided by the RPM Respiratory Gating System. The system sorts, or bins, the images based on the point in the respiratory cycle at which they were acquired. Using the binned images, the system can reconstruct volumetric CT images that minimize the motion artifacts appearing in the traditional CT images. [25] [26]



**Figure 6:** The topogram image of the CT scan on the left was taken without any form of gating, and shows numerous motion artifacts. The topogram image of the CT scan on the right was acquired using respiration synchronized CT, and shows a clear image of the target volume. (Images courtesy Virginia Commonwealth University, Richmond, Virginia, USA).

There are two different approaches to 4D-CT image acquisition: prospective and retrospective. During a prospective 4D-CT simulation, the CT scanner collects images only at one phase, or portion, of a patient's normal respiratory cycle. Instead of scanning continuously, the system takes a series of snapshots at the proper phase, moves the couch to the next position, takes more snapshots, and so on. Basically, prospective 4D-CT results in one volumetric CT image collected at a specific phase of the respiratory cycle.

In contrast, retrospective 4D-CT produces multiple volumetric CT images, each representing one phase of the respiratory cycle. The system collects images continuously during all phases, while the couch remains stationary. Each acquired image has a phase stamp so that after collecting the images, the system can bin them based on the phase of the respiratory cycle in which they were collected. Each phase is then separately reconstructed. Meanwhile the couch moves to the next position and more images are collected continuously. This process is repeated until the entire volume of interest is scanned and reconstructed.



**Figure 7:** Beam's Eye Views of gated and non-gated treatment volumes in the Eclipse treatment planning system (Images courtesy AZ Sint Augustinus, Wilrijk, Belgium).

In the steps of the clinical radiation therapy process that lead up to treatment planning, imaging is performed with the intent of clearly visualizing the target volume. The payoff of using image-guided motion management comes in the treatment planning stage, because target volumes and critical structures can be contoured with smaller margins that account for the actual motion.

### **Post-Planning Verification: Integrated Simulation and Verification**

Before treatment, clinicians can use the new Acuity system to help ensure that treatment plans will achieve the intended results. Acuity integrates verification software tools for dynamically tracking tumor motion during the verification process. It produces filmless, high-resolution, radiographic and fluoroscopic images of patients in their treatment positions. Clinicians can then evaluate the treatment plan by observing the patient's position and respiratory motion with the overlaid fields and determining whether that motion will remain within the treatment field margins. Any necessary adjustments to the plan can be made and re-verified quickly. [27] [28]



**Figure 8** The Acuity simulation and verification system



**Figure 9** Portal Vision electronic portal imaging system with robotic support arm.

### Review of Imaging in the Treatment Room

The latest advances in imaging technology can help clinicians to obtain more information about the target volume position and to correct for changes in its position at the time of treatment. By using image-guided motion management during 3D-CRT and IMRT, clinicians can more accurately control the dose delivered to the tumor while reducing exposure to the surrounding healthy tissue.

Early studies based on port films indicated the benefits of portal verification [29] [30]. Numerous subsequent studies have characterized the magnitude and nature of setup errors for a variety of clinical conditions. Weekly port films are the routine clinical standard for ensuring accurate targeting of external beam radiation therapy [31]. Random and systematic errors of up to 6 mm ( $\sigma$ ) have been reported in such studies [32]. The modern era of electronic portal imaging devices (EPIDs) began in the early 1980s with demonstration by the late Norman Baily of the use of a fluoroscopic system to acquire megavoltage transmission images [33]. The introduction of the scanning liquid ionization chamber system in 1990 [34] was quickly followed by the introduction of camera-based fluoroscopic EPIDs from other manufacturers.

The importance of geometric accuracy has driven the development of imagers that can monitor treatment accuracy more effectively than weekly port filming [35] [36] with minimal increase in workload [37]. An EPID can acquire images automatically with near real-time display, store them digitally, and provide quantitative analysis tools. Studies have shown that increased portal imaging frequency can reveal daily variations in patient alignment that are not observed with weekly filming [38] [39]. Furthermore, an EPID can provide immediate patient alignment information, without the delay involved in processing a film. Instant image availability enables the development of on-line correction protocols and daily targeting adjustments. [40] [41] In addition to aiding acquisition, the digital nature of EPIDs can be exploited to enhance the portal review process. Studies have examined the process of subjective portal image evaluation by clinicians and have found a wide variation among reviewers in reporting setup deviations in portal images [42] [43]. Many EPID systems offer computer-assisted image review with anatomy-matching routines and quantitative alignment analysis.

Investigations of internal organ motion [44] [45] [46] have demonstrated that, for many sites, substantial reductions in geometric uncertainty require the visualization of internal structures in the reference frame of the treatment machine. The development of volumetric imaging systems for online image guidance has been a major focus of research in the past 5 years. Many investigators have examined the use of the

treatment beam to perform megavoltage computed tomography (MV-CT) of the patient in treatment position. This was first demonstrated in 1983 by Swindell et al [47] and was extended to cone-beam implementations by 1998 [48] [49]. Brahme et al. proposed the development of MV CT based on the 50-MV scanning photon beam of the racetrack microtron; [50] this approach offers elevated contrast due to the increased pair-production cross-section. Although many investigators have been evaluating MV CT for radiotherapy verification, the only system to reach routine clinical use is the one developed by Nakagawa et al. [51] In their procedure, a pre-treatment MV CT slice is used to verify the patient setup for stereotactic radiosurgery of the lung. Although utilization of the MV source for imaging seems to offer an elegant solution in terms of imaging and delivery with the same source, it faces the enormous challenge posed by the poor detection efficiency of X-ray detectors in the MV energy range [52]. The low efficiency results in poor signal-to-noise performance for clinically acceptable doses (10cGy). Furthermore, the increased radiation transport in the X-ray detector reduces the spatial resolution that can be expected at these energies.

Introducing kilovoltage-imaging technologies into the therapy setting is another alternative. The clear value of integrated imaging and delivery compelled Uematsu et al. to install a conventional CT scanner and a conventional simulation unit in the radiotherapy suite [53]. This approach offers volumetric CT, real-time fluoroscopy and radiographic imaging in the treatment room. Reference between the three is maintained through a single, pivoting table that can dock to each system. This approach has been employed in a variety of anatomic sites, demonstrating the many advantages of integrated imaging and delivery.

### **The PortalVision Electronic Portal Imaging System**

The Varian PortalVision™ electronic portal imaging system creates high-resolution, two-dimensional electronic images using the megavoltage treatment beam, and compares them to the digitally reconstructed radiographs (DRRs) from the treatment planning system or the digital images from the Acuity simulator. This comparison is done for two purposes: verification of the patient setup and verification of individual field placements. Electronic portal imaging systems are in routine clinical use at many institutions and are increasingly being used to measure setup errors [54]. The introduction of amorphous silicon flat panel imagers has been demonstrated to produce better portal images using less dose [55]. The improvement in image quality has also enabled the practical use of implanted radiopaque markers for on-line corrective positioning [56].

Also, the dosimetric capabilities of PortalVision allow clinicians to convert the electronic image into a dose distribution and then compare the acquired portal dose to the predicted portal dose from the planning system. Quantitative comparisons can be performed for machine quality assurance (QA), for verifying MU calculations [57] or for pre-treatment verification of IMRT fluence distributions [58].

### **Description of On-Board Imager™, Its Intended Functions and Purpose**

Varian Medical Systems has recently introduced the On-Board Imager, for the Clinac® and Trilogy™ medical linear accelerators. It is designed to improve the precision and effectiveness of cancer treatments by providing tools to target and track tumors more accurately. The On-Board Imager will enable clinicians to obtain high-resolution X-ray images to pinpoint tumor sites, to register those images against reference (planning) images, to adjust patient positioning automatically when necessary, and to complete treatment delivery, all within the standard daily treatment time slot.

Varian's approach is to integrate a kilovoltage (kV) X-ray source and large-area flat-panel detector on a medical linear accelerator for fluoroscopy, radiography, and volumetric cone-beam CT. In effect this combines the imaging capabilities of a digital simulator, a CT scanner into the linac. In this highly integrated form, the control system orchestrates the interplay of the imaging and delivery components in a single machine. Such an approach offers the flexibility to employ a treatment-procedure-specific imaging strategy, whether real-time fluoroscopy, radiography, cone-beam CT, or an appropriate combination of all three. Integration will allow image-guided procedures to be performed within the tight time constraints found in the radiation therapy setting.



**Figure 10:** Clinac with On Board Imager. The system incorporates of an X-ray tube and an amorphous-silicon flat-panel image detector on a pair of robotic arms. (Image courtesy Emory University, Atlanta, Georgia, USA).

Varian's On-Board Imager is mounted on the treatment machine gantry via two robotically controlled arms; each operate along three axes of motion, so that they can be positioned optimally for the best possible imaging of the target volume or the motion of other internal structures some distance away. The arms also allow the imager to be quickly retracted out of the way when not in use. The kV imaging system operates in a plane orthogonal to the megavoltage treatment beam and its associated amorphous silicon imager. Thus the two imagers can be used on concert.

The amorphous silicon flat-panel X-ray image detectors yield digital images showing internal anatomic landmarks with a high degree of precision. Software tools are incorporated that allow rapid manual or automated image matching to reference images of the patient position used in treatment planning. By rotating the gantry 90 degrees two coherent kV images can be quickly acquired. Alternatively the image pair can consist of a kV image and orthogonal MV image acquired in rapid succession without rotating the gantry. The imaging software then registers that image pair against a corresponding reference image pair. The reference images can be radiographs acquired on a simulator or they can be DRR images computed from the volumetric CT data set used in treatment planning. The image registration software takes advantage of common or coherent information in each image pair to search for the position and angular correction needed to minimize the difference in mutual information contained within the reference image set and the daily image set. This in-plane mutual information matching can be restricted to a user specified region of interest if desired. The result from this 2D + 2D anatomical matching is a computed offset with 5 degrees of freedom. The needed X, Y and Z translations plus the in-plane rotations (pitch and yaw) are automatically computed. The matched image sets are then overlaid with suitable tools for visual confirmation. Once the match is accepted the corrected position offsets are automatically downloaded so that the couch can be repositioned from outside the treatment vault.

In addition to anatomic matching, automated tools are provided for matching the position of implanted radiopaque fiducial markers using similar kV image pairs. The planning volumetric CT data set is acquired after implanting suitable gold fiducial markers. The Varian software is used to quickly search the 3D CT data to locate the marker positions corresponding to the PTV. Each treatment day, a pair of kV transmission images is acquired as described above. The imaging software provided automatically locates the markers in each of those two images and registers those locations against the corresponding 3D coordinates of the same markers in the reference CT data set. From this, a full six-degree of freedom (6DOF) correction vector is computed. Again, after review and acceptance of the match the couch position can be automatically corrected. In this way soft tissue structures or target volumes such as the prostate can be quickly targeted using low dose radiographic imaging on a daily basis.

Operating in the fluoroscopic mode, the image detector can track real-time anatomic motion and thus provide a clear indication of how a tumor will move during treatment due to respiration or other normal physiological processes. This modality can be used in concert with Varian's RPM™ respiratory gating system to confirm the intended beam gating periods and the resulting margins immediately prior to each treatment. This may prove for example to be a useful tool as part of an extra-cranial radiosurgery or radioablation program. Real-time tracking algorithms have been demonstrated that are anticipated to be useful in directly providing respiratory gating or tracking information from internal anatomic motion.

Possibly the most powerful imaging modality this system incorporates is Cone Beam CT. In this mode an entire volumetric CT data set is reconstructed with a single gantry rotation. The system takes full advantage of the new PaxScan 4030CB amorphous silicon flat panel imager. That imager utilizes unique technology to provide the high dynamic range, sensitivity, and frame rates needed for these applications. Varian has also incorporated a unique 150 kV X-ray tube designed specifically for this application.

By using robotic technology and control software to position the On-Board Imager and patient couch, the total system offers the automation, speed, and flexibility needed to make the IGRT process clinically practical. The system is designed for full integration with Varian's VARiS Vision™ image and information management system as well as the company's Eclipse™ treatment planning software products.

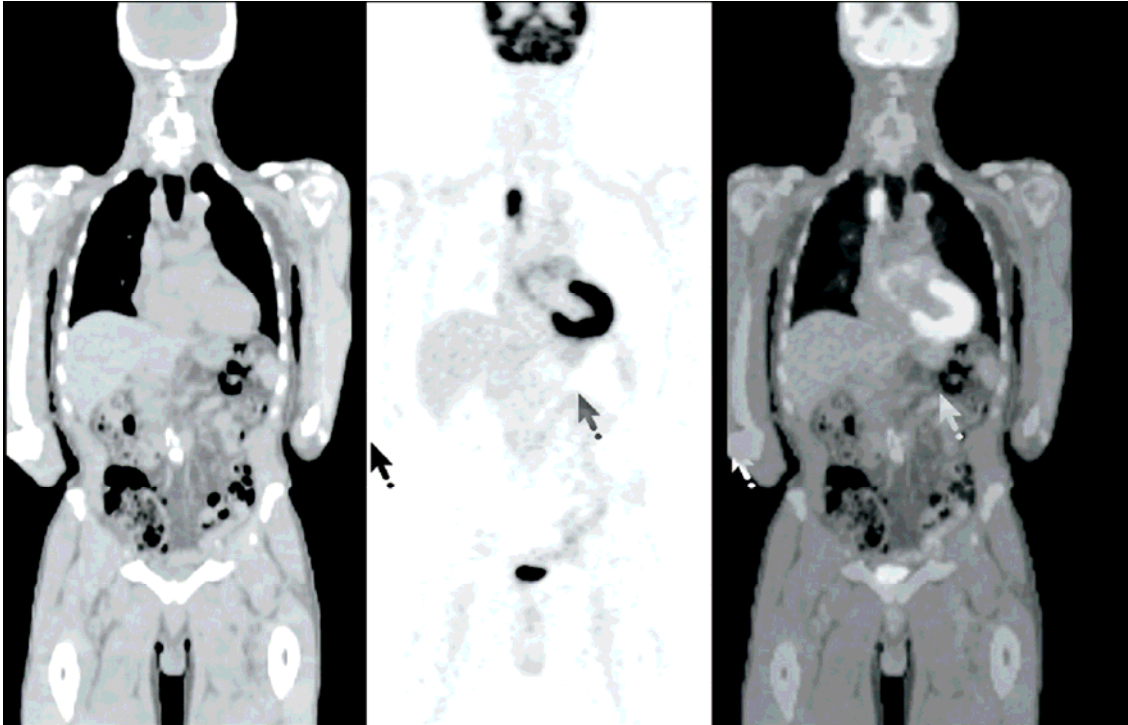
The new On-Board Imager will be available as an option on all of Varian's newly installed high-energy Clinac linear accelerators, and as an upgrade for most digital Clinac accelerators already in place at clinical sites. It will be a standard feature on all Trilogy linear accelerators. Several systems are now in clinical use.

## **A Look Ahead**

So far, the imaging techniques discussed have focused on shrinking the margin around the target volume. However, the use of functional imaging can influence the way in which clinicians define the target volume itself. Clinical researchers at the Memorial Sloan-Kettering Cancer Center have developed the concept of a biological, or functional, target volume that is derived from biological images and used to guide customized dose delivery to various parts of the treatment volume [59].

Functional imaging techniques, such as magnetic resonance spectroscopy (MRS), positron emission tomography (PET), and single photon emission computed tomography (SPECT), provides metabolic, or other functional data indicating the location, size, and aggressiveness of disease. These techniques may help clinicians observe functional changes so that they can create targeted treatment plans that deliver escalated doses to the most metabolically active parts of a tumor.

For example, Figure 11 below shows a PET and CT image of a lung cancer case. Based on the combined functional PET image and the anatomical CT image, clinicians may localize cancerous regions even before they are physically evident. Then, by using motion management techniques, they can treat the small lesions with a higher dose. Likewise, clinicians may use SPECT or MRI to identify functional lesions of interest, and then differentially dose the lesions with IMRT based on that functional information.



**Figure 11:** These diagnostic images of a lung cancer case were created using a Discovery LS scanner from GE Medical Systems, which combines PET and CT scanning in a single machine. On the left, a CT image shows anatomical detail, but the cancer is hard to see. In the central PET image, cancer shows up distinctly as a spot on the lung, but anatomical detail is hard to see. On the right, a fused PET/CT image can help doctors precisely localize the cancerous tumor.

Motion artifacts in PET images caused by respiration are an important factor in degrading PET image quality and quantification. Motion artifacts lead to two major effects: First, they affect the accuracy of quantification, producing a reduction of the measured standard uptake value (SUV). Second, the apparent lesion volume is overestimated. Both impact upon the usage of PET images for radiation treatment planning. The first affects the visibility, or contrast, of the lesion. The second results in an increase in the planning target volume, and consequently a greater radiation dose to the normal tissues. One way to compensate for this effect is by acquiring the PET data in synchronization with the respiratory motion [60].

#### **Toward Increasing Accuracy of Tumor Targeting**

The combination of IMRT and IGRT has the potential to achieve both unparalleled tumor control and normal tissue sparing. To confidently administer highly conformal radiation to complex three-dimensional volumes, clinicians can track and manage tumor motion in all four dimensions by using Dynamic Targeting, an approach toward image-guided motion management that reduces uncertainties in both setup and organ motion. Achieving image-guided motion management throughout the radiation oncology process requires not only a single product, but a suite of integrated products to manipulate all patient data, including images, efficiently and effectively.

#### **REFERENCES**

1. Porter A, Aref A, Chodounsky Z, Elzawawy A, Manatrakul N, Ngoma T, Orton C, Van't Hooff E, Sikora K.. 1999. A global strategy for radiotherapy: a WHO consultation. *Clinical Oncology*. **11**(6): 368-70.
2. Mohan R, Wu Q, Manning M, Schmidt-Ullrich R. 2000. Radiobiological considerations in the design of fractionation strategies for intensity-modulated radiation therapy of head and neck cancers. *International Journal of Radiation Oncology Biology Physics*. **46**(3): 619-30.

3. Saunders M, Dische S, Barrett A, Harvey A, Griffiths G, Palmar M. 1999. CHART (continuous, hyper-fractionated, accelerated radiotherapy): a tale of two disciplines. *British Journal of Cancer*. **80** Suppl 1:110-5.
4. Read G. 1998. Conformal radiotherapy: a clinical review. *Clinical Oncology (R Coll Radiol)*. **10**(5): 288-96.
5. Zelefsky MJ, Fuks Z, Hunt M, Yamada Y, Marion C, Ling CC, Amols H, Venkatraman ES, Leibel SA. 2002. High-dose intensity modulated radiation therapy for prostate cancer: early toxicity and biochemical outcome in 772 patients. *International Journal of Radiation Oncology Biology Physics*. **53**(5): 1111-6.
6. Hunt MA, Zelefsky MJ, Wolden S, Chui CS, LoSasso T, Rosenzweig K, Chong L, Spirou SV, Fromme L, Lumley M, Amols HA, Ling CC, Leibel SA. 2001. Treatment planning and delivery of intensity-modulated radiation therapy for primary nasopharynx cancer. *International Journal of Radiation Oncology Biology Physics*. **49**(3): 623-32.
7. Marks JE, Haus AG. 1976. The effect of immobilization on localization error in the radiotherapy of head and neck cancer. *Clinical Radiology*. **27**(2):175-77
8. Goitein M, Busse J. 1975. Immobilization error: some theoretical considerations. *Radiology*. **117**: 407-12.
9. Killoran JH, Kooy HM, Gladstone DJ, Welte FJ, Beard CJ. 1997. A numerical simulation of organ motion and daily setup uncertainties: implications for radiation therapy. *International Journal of Radiation Oncology Biology Physics*. **37**(1): 213-21.
10. Langen KM, Jones DT. 2001. Organ motion and its management. *International Journal of Radiation Oncology Biology Physics*. **50**(1): 265-78.
11. Booth JT, Zavgorodni SF. 1999. Set-up error & organ motion uncertainty: a review. *Australasia Physics Engineering Science & Medicine*. **22**(2): 29-47
12. Verhey LJ. 1995. Immobilizing and Positioning Patients for Radiotherapy. *Seminars in Radiation Oncology*. **5**(2): 100-114.
13. Kutcher GJ, Mageras GS, Leibel SA 1995. Control, Correction, and Modeling of Setup Errors and Organ Motion. *Seminars in Radiation Oncology*. **5**(2): 134-145.
14. Misfeldt J, Chessman M. 1999. Advances in Patient Positioning. *Journal of Oncology Management*. **8**(2): 14-6.
15. Suramo I, Paivansalo M, Myllyla V. 1984. Cranio-caudal movements of the liver, pancreas and kidneys in respiration. *Acta Radiology Diagnostics (Stockholm)*. **25**(2): 129-31.
16. Hanley J, Debois MM, Mah D, Mageras GS, Raben A, Rosenzweig K, Mychalczak B, Schwartz LH, Gloeggler PJ, Lutz W, Ling CC, Leibel SA, Fuks Z, Kutcher GJ. 1999. Deep inspiration breath-hold technique for lung tumors: the potential value of target immobilization and reduced lung density in dose escalation. *International Journal of Radiation Oncology Biology Physics*. **45**(3): 603-11.
17. Mah D, Hanley J, Rosenzweig KE, Yorke E, Braban L, Ling CC, Leibel SA, Mageras G. 2000. Technical aspects of the deep inspiration breath-hold technique in the treatment of thoracic cancer. *International Journal of Radiation Oncology Biology Physics*. **48**(4): 1175-85.
18. Wong JW, Sharpe MB, Jaffray DA, Kini VR, Robertson JM, Stromberg JS, Martinez AA. 1999. The use of active breathing control (ABC) to reduce margin for breathing motion. *International Journal of Radiation Oncology Biology Physics*. **44**(4): 911-9.
19. Blomgren H, Lax I, Naslund I, Svanstrom R. 1995. Stereotactic high dose fraction radiation therapy of extracranial tumors using an accelerator. Clinical experience of the first thirty-one patients. *Acta Oncology*. **34**(6): 861-70.

20. Kubo HD, Hill BC. 1996. Respiration gated radiotherapy treatment: a technical study. *Physics Medicine Biology*. **41**(1): 83-91.
21. Kubo HD, Wang L. 2000. Compatibility of Varian 2100C gated operations with enhanced dynamic wedge and IMRT dose delivery. *Medical Physics*. **27**(8): 1732-8.
22. Kubo HD, Len PM, Minohara S, Mostafavi H. 2000. Breathing-synchronized radiotherapy program at the University of California Davis Cancer Center. *Medical Physics*. **27**(2): 346-53.
23. Ramsey CR, Cordrey IL, Oliver AL. 1999. A comparison of beam characteristics for gated and nongated clinical x-ray beams. *Medical Physics*. **26**(10): 2086-91.
24. Ramsey CR, Scaperoth D, Arwood D, Oliver AL. 1999. Clinical efficacy of respiratory gated conformal radiation therapy. *Medical Dosimetry*. **24**(2): 115-9.
25. Ford EC, Mageras GS, Yorke E, Ling CC. 2003. Respiration-correlated spiral CT: a method of measuring respiratory-induced anatomic motion for radiation treatment planning. *Medical Physics*. **30**(1): 88-97.
26. Vedam SS, Keall PJ, Kini VR, Mostafavi H, Shukla HP, Mohan R. 2003. Acquiring a four-dimensional computed tomography dataset using an external respiratory signal. *Physics in Medicine and Biology*. **48**(1): 45-62.
27. Mageras GS, Yorke E, Rosenzweig K, Braban L, Keatley E, Ford E, Leibel SA, Ling CC. 2001. Fluoroscopic evaluation of diaphragmatic motion reduction with a respiratory gated radiotherapy system. *Journal of Applied Clinical Medical Physics*. **2**(4): 191-200.
28. Chen QS, Weinhaus MS, Deibel FC, Ciezki JP, Macklis RM. 2001. Fluoroscopic study of tumor motion in breathing: facilitating precise radiation therapy for lung cancer patients. *Medical Physics*. **28**(9): 1850-6.
29. Rabinowitz I, Broomberg J, Goitein M, McCarthy K, Leong J. 1985. Accuracy of radiation field alignment in clinical practice. *International Journal of Radiation Oncology Biology Physics*. **11**(10): 1857-67.
30. Rosenthal SA, Galvin JM, Goldwein JW, Smith AR, Blitzer PH. 1992. Improved methods for determination of variability in patient positioning for radiation therapy using simulation and serial portal film measurements. *International Journal of Radiation Oncology Biology Physics*. **23**(3): 621-5.
31. Byhardt RW, Cox JD, Hornburg A, Liemann G. 1978. Weekly localization films and detection of field placement errors. *International Journal of Radiation Oncology Biology Physics*. **4**(9-10): 881-7.
32. Balter JM, Sandler HM, Lam K, Bree RL, Lichter AS, ten Haken RK. 1995. Measurement of prostate movement over the course of routine radiotherapy using implanted markers. *International Journal of Radiation Oncology Biology Physics*. **31**(1): 113-8.
33. Baily NA, Horn RA, Kampp TD. 1980. Fluoroscopic visualization of megavoltage therapeutic x ray beams. *International Journal of Radiation Oncology Biology Physics*. **6**(7): 935-9.
34. Meertens H, van Herk M, Bijhold J, Bartelink H. 1990. First clinical experience with a newly developed electronic portal imaging device. *Int Journal of Radiation Oncology Biology Physics*. **18**(5): 1173-81.
35. Boyer AL, Antonuk L, Fenster A, Van Herk M, Meertens H, Munro P, Reinstein LE, Wong J. 1992. A review of electronic portal imaging devices (EPIDs). *Medical Physics*. **19**(1): 1-16.
36. Leong J. 1986. Use of digital fluoroscopy as an on-line verification device in radiation therapy. *Physics in Medicine and Biology*. **31**(9): 985-92.

37. Michalski JM, Graham MV, Bosch WR, Wong J, Gerber RL, Cheng A, Tinger A, Valicenti RK.. 1996. Prospective clinical evaluation of an electronic portal imaging device. *International Journal of Radiation Oncology Biology Physics*. **34**(4): 943-51.
38. Valicenti RK, Michalski JM, Bosch WR, Gerber R, Graham MV, Cheng A, Purdy JA, Perez CA. 1994. Is weekly port filming adequate for verifying patient position in modern radiation therapy? *International Journal of Radiation Oncology Biology Physics*. **30**(2): 431-8.
39. Herman MG, Abrams RA, Mayer RR. 1994. Clinical use of on-line portal imaging for daily patient treatment verification. *International Journal of Radiation Oncology Biology Physics*. **28**(4): 1017-23.
40. Balter JM, Chen GT, Pelizzari CA, Krishnasamy S, Rubin S, Vijayakumar S. 1993. Online repositioning during treatment of the prostate: a study of potential limits and gains. *International Journal of Radiation Oncology Biology Physics*. **27**(1): 137-43.
41. Bel A, van Herk M, Bartelink H, Lebesque JV. 1993. A verification procedure to improve patient set-up accuracy using portal images. *Radiotherapy Oncology*. **29**(2): 253-60.
42. Bissett R, Boyko S, Leszczynski K, Cosby S, Dunscombe P, Lightfoot N. 1995. Radiotherapy portal verification: an observer study. *British Journal of Radiology*. **68**(806): 165-74.
43. Perera T, Moseley J, Munro P. 1999. Subjectivity in interpretation of portal films. *International Journal of Radiation Oncology Biology Physics*. **45**(2): 529-34.
44. Roeske JC, Forman JD, Mesina CF, He T, Pelizzari CA, Fontenla E, Vijayakumar S, Chen GT. 1995. Evaluation of changes in the size and location of the prostate, seminal vesicles, bladder, and rectum during a course of external beam radiation therapy. *Int Journal of Radiation Oncology Biology Phys*. **33**(5): 1321-9.
45. Lattanzi J, McNeeley S, Pinover W, Horwitz E, Das I, Schultheiss TE, Hanks GE. 1999. A comparison of daily CT localization to a daily ultrasound-based system in prostate cancer. *International Journal of Radiation Oncology Biology Physics*. **43**(4): 719-25.
46. Van Herk M, Bruce A, Kroes AP, Shouman T, Touw A, Lebesque JV. 1995. Quantification of organ motion during conformal radiotherapy of the prostate by three dimensional image registration. *International Journal of Radiation Oncology Biology Physics*. **33**(5): 1311-20.
47. Swindell W, Simpson RG, Oleson JR, Chen CT, Grubbs EA. 1983. Computed tomography with a linear accelerator with radiotherapy applications. *Medical Physics*. **10**(4): 416-20.
48. Mosleh-Shirazi MA, Evans PM, Swindell W, Webb S, Partridge M. 1998. A cone-beam megavoltage CT scanner for treatment verification in conformal radiotherapy. *Radiotherapy and Oncology*. **48**(3): 319-28
49. Hesse BM, Spies L, Groh BA. 1998. Tomotherapeutic portal imaging for radiation treatment verification. *Physics in Medicine and Biology*. **43**(12): 3607-16.
50. Brahme A, Lind B, Nafstadius P. 1987. Radiotherapeutic computed tomography with scanned photon beams. *International Journal of Radiation Oncology Biology Physics*. **13**(1): 95-101.
51. Nakagawa K, Aoki Y, Tago M, Terahara A, Ohtomo K. 2000. Megavoltage CT-assisted stereotactic radiosurgery for thoracic tumors: original research in the treatment of thoracic neoplasms. *International Journal of Radiation Oncology Biology Physics*. **48**(2): 449-57.
52. Groh BA, Siewerdsen JH, Drake DG, Wong JW, Jaffray DA. 2002. A performance comparison of flat-panel imager-based MV and kV cone-beam CT. *Medical Physics*. **29**(6): 967-75.

53. Uematsu M, Shioda A, Tahara K, Fukui T, Yamamoto F, Tsumatori G, Ozeki Y, Aoki T, Watanabe M, Kusano S. 1998. Focal, high dose, and fractionated modified stereotactic radiation therapy for lung carcinoma patients: a preliminary experience. *Cancer*. **82**(6): 1062-70.
54. Hurkmans CW, Remeijer P, Lebesque JV, Mijnheer BJ. 2001. Set-up verification using portal imaging; review of current clinical practice. *Radiotherapy Oncology*. **58**(2): 105-20.
55. Kruse JJ, Herman MG, Hagness CR, Davis BJ, Garces YI, Haddock MG, Olivier KR, Stafford SL, Pisansky TM. 2002. Electronic and film portal images: a comparison of landmark visibility and review accuracy. *International Journal of Radiation Oncology Biology Physics*. **54**(2): 584-91.
56. Herman MG, Pisansky TM, Kruse JJ, Prisciandaro JI, Davis BJ, King BF. 2003. Technical aspects of daily online positioning of the prostate for three-dimensional conformal radiotherapy using an electronic portal imaging device. *International Journal of Radiation Oncology Biology Physics*. **57**(4): 1131-40.
57. Pasma KL, Kroonwijk M, Quint S, Visser AG, Heijmen BJ. 1999. Transit dosimetry with an electronic portal imaging device (EPID) for 115 prostate cancer patients. *International Journal of Radiation Oncology Biology Physics*. **45**(5): 1297-303.
58. Van Esch A, Depuydt T, Huyskens DP. 2004. The use of an aSi-based EPID for routine absolute dosimetric pre-treatment verification of dynamic IMRT fields. *Radiotherapy Oncology*. **71**(2): 223-34.
59. Ling CC, Humm J, Larson S, Amols H, Fuks Z, Leibel S, Koutcher JA. 2000. Towards multidimensional radiotherapy (MD-CRT): biological imaging and biological conformality. *International Journal of Radiation Oncology Biology Physics*. **47**(3): 551-60.
60. Nehmeh SA, Erdi YE, Ling CC, Rosenzweig KE, Squire OD, Braban LE, Ford E, Sidhu K, Mageras GS, Larson SM, Humm JL. 2002. Effect of respiratory gating on reducing lung motion artifacts in PET imaging of lung cancer. *Medical Physics*. **29**(3): 366-71.