Functional Imaging in the Modern Radiation Oncology Practice—The Role of Positron Emission Tomography/Computed Tomography-based Treatment Planning

a report by
Dwight E Heron, MD

Associate Professor, University of Pittsburgh Cancer Institute, University of Pittsburgh School of Medicine

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Technological advances in the field of radiation oncology over the last decade have revolutionized care for cancer patients in the US and worldwide. These technological advancements have been both hardware- and software-based. More importantly, however, a major shift in the clinical paradigm exemplifies this ground-breaking change. Innovative approaches incorporating both technological and clinical changes have resulted in a complex and elegant mix of imaged-based approaches using computed tomography (CT), magnetic resonance, and positron emission tomography (PET). These are used in conjunction with treatment delivery techniques including intensity-modulated radiation therapy (IMRT), image-guided brachytherapy, and adaptive treatment approaches—image-guided radiation therapy (IGRT) and adaptive radiation therapy (ART). Central to the success of any local therapy is the accurate diagnosis of tumor extent. Functional imaging, especially PET-CT, is being increasingly incorporated into the oncological management of a variety of cancer diagnoses. Its use in the modern radiation oncology practice is only now being realized. This review will focus on the implementation of PET-CT in staging, treatment plan design, and assessment of response in radiation oncology.

Principles of Positron Emission Tomography

PET uses a short-lived radiotracer that upon decay emits a positron—the antimatter counterpart of an electron. The positron is a highly unstable particle that almost instantaneously encounters an electron in a process called annihilation. This results in two gamma photons of 511 keV being emitted perpendicular to each other. This decay can be recognized by a ring of detectors that are able to localize the origin of each positron, thus creating a map of activity proportional to metabolic differences. Since there is an altered metabolic characteristic of tumor cells compared with surrounding normal tissues, an 'activity map' can be created reflecting the differing regions within the body. The uncontrolled cellular proliferation, which is the hallmark of malignant transformation, offers the perfect target for the diagnosis and evaluation of a variety of cancers. 2-[18F]-fluoro-2-deoxy-D glucose (FDG), a glucose analog, is the most commonly used radiotracer. This tracer, administered intravenously, is transported from the extra-cellular compartment to the intra-cellular compartment by the membrane-bound glucose transporter. Once intra-cellular, FDG is phosphorylated by hexokinase to form FDG-6-PO4 in proportion to the glycolytic rate of the cell (see *Figure 1*). Unlike glucose-6-PO4, the normal metabolite of hexokinase, FDG-6-PO4 cannot enter the glycolytic pathways and therefore accumulates intra-cellularly. As a result, this differential accumulation can be quantified and used to form an image of tumor deposits at the primary site as well as at more distant sites. A variety of other tracers are used to image hypoxia (18[F]fluoromisonidazole), proliferation ((18[F]-fluorothymidine), oxygenation (oxygen-15), and angiogenesis.

Dwight E Heron, MD, is an Associate Professor in the University of Pittsburgh School of Medicine and Vice Chairman of Clinical Affairs in the Department of Radiation Oncology at the University of Pittsburgh Medical Center Cancer Centers. Dr Heron is the primary investigator for National Cancer Institute grants for a Cancer Disparities Research Partnership and for the Center to Reduce Cancer Disparities Patient Navigator Program. His clinical and research interests include the integration of advanced imaging in oncology, such as positron emission tomography/computed tomography (CT) and 4-D CT, which are used in modern radiation treatment planning, and their delivery as cranial and body radiosurgery. He is the author and co-author of numerous journal articles, book chapters, monographs, and abstracts and continues to teach and mentor medical students and resident in the tradition of the biopsychosocial model.

Why PET-CT Simulation?

Beginning in the early 1980s and escalating in subsequent years, functional imaging and specifically PET has gained increasing importance in the diagnosis and staging of a variety of malignancies, including lymphomas, head and neck cancers, lung and esophageal cancers, melanomas, brain tumors, and gastro-intestinal cancers. Using FDG as the primary tracer, numerous studies have demonstrated the superiority of PET over CT in a variety of disease states. Although useful in diagnosis and staging, stand-alone PET images have a less than optimal role in radiation treatment planning, predominantly because of their lack of anatomical information. Modern radiation therapy treatment planning is currently based on computed tomography with three-dimensional reconstructions, known as 3-D conformal radiation therapy (3D-CRT). Complementary imaging modality such as magnetic resonance imaging (MRI) and single photon emission computed tomography (SPECT), among others, can be fused with the simulation CT to aid in target or normal tissue definition. Given its lack of the customary anatomical detail necessary for conformal radiation therapy, stand-alone PET has been difficult to use for planning purposes. Furthermore, the lack of a simple methodology to fuse the PET dataset with the simulation CTs dataset has limited the role of these systems in radiation oncology.

Townsend et al. at the University of Pittsburgh first envisioned the integration of PET and CT and created the prototype of the modern commercial systems. These hybrid systems avoid the limitation of stand-alone PET systems by the acquisition of the CT (anatomical) and PET (biological/physiological) data using the same gantry and table without resorting to software-based fusion, which has its own set of limitations. The implementation of these systems in lieu of the conventional CT simulation eliminates the step of having to fuse the PET-CT dataset with a CT

Figure 1: Mechanism of FDG Metabolism and Detection in Functional Imaging Using PET-CT

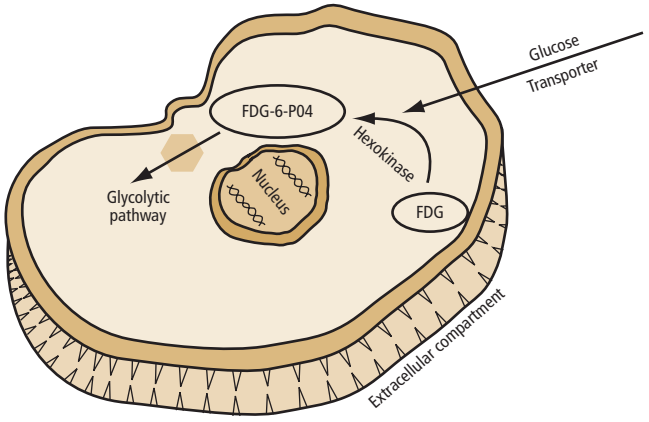

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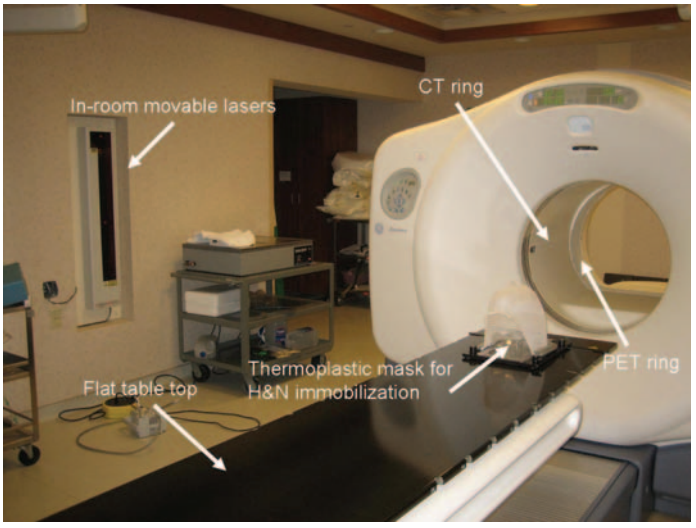
Figure 2: PET-CT Simulator Depicting a Modified Table-top, Immobilization Devices, and In-room Lasers



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simulation dataset. By definition, the CT from the PET-CT study is the CT simulation. An image of this set-up is depicted in *Figure 2*.

Outcome Studies Using PET and PET-CT in Oncology

The use of PET-CT for radiation treatment planning is a relatively recent phenomenon. Nonetheless, it is clear that the success of highly conformal therapies such as IMRT necessitates increasingly greater degrees of target definition, as is afforded by PET-CT. The steep dose gradients typical of an IMRT plan require that the location of the target be clearly delineated. Due to the complex interplay of conformance and inhomogeneity of IMRT planning, failure to accurately delineate the known disease can severely compromise the plan by underdosing the intended gross disease or overdosing the nearby critical structures. A number of studies have evaluated the impact on PET-CT on target definition but very few have reported results of its impact on outcomes. Below is a summary of the results of PET-CT on target definition and, where available, clinical outcome measures in six common diseases seen in the modern radiation oncology practice.

Head and Neck Cancers

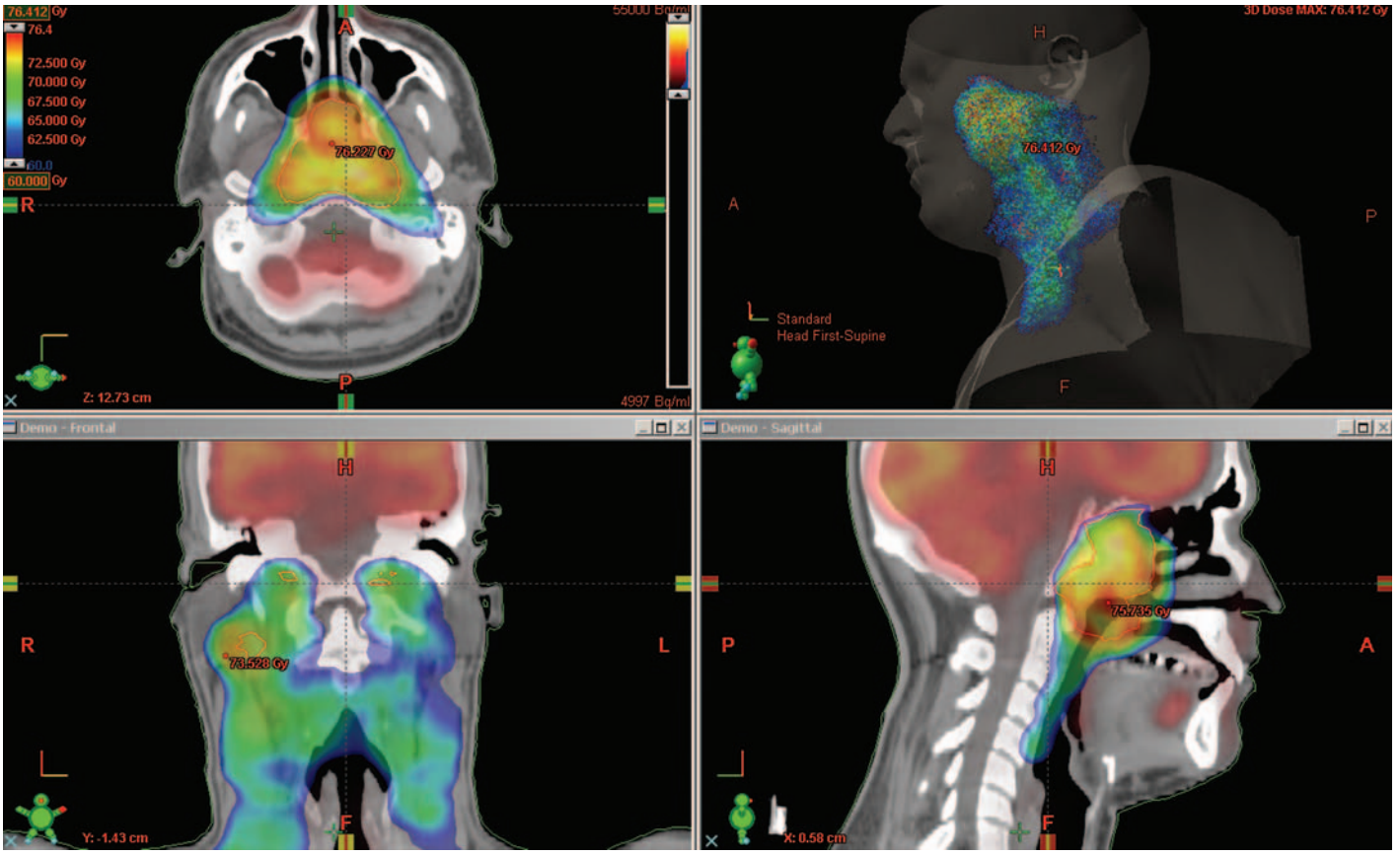
Nowhere is the need for highly conformal techniques more obvious than in the treatment of head and neck cancers. Multiple sensitive structures including the major and minor salivary glands, mandible, spinal cord, and brainstem have made IMRT the modality of choice in treating these cancers. The close proximity of these critical structures to both tumor-bearing areas and nodal basins requires accurate identification of tumor-bearing regions if undue toxicities are to be avoided. Riegel et al. have reported on the variability of tumor volume definition in CT- versus PET-CT-based target definition. In general, they found significant inter-observer difference with a tendency to contour larger volumes on CT than on fused PET-CT. Similarly, the author found that PET-CT simulation gross tumor volumes (GTVs) were on average three times smaller than their CT-only counterparts, and that that PET-CT identified a greater number of tumor bearing nodal areas compared with CT alone.[1]

There are very few studies evaluating the impact of functional imaging on outcome in head and neck cancer patients. Koike et al. used FDG-PET to predict tumor regrowth after definitive radiation in 20 patients.[2] All patients underwent pre-treatment PET and post-treatment PET within 10 days after completion of radiation therapy. These early PET studies seem to indicate the ability to predict those who are likely to harbor residual disease three months after treatment. If replicated, this could be a potentially powerful tool in predicting early regrowth of malignancy. Similarly, Andrade et al. used a more conventional surveillance pattern of six to eight weeks for post-treatment scans. In that study, 28 patients with a median follow-up of 17.6 months underwent pre-treatment and post-treatment PET-CT imaging on a three-month basis as surveillance. They found that the sensitivity and specificity of detecting residual disease was higher in PET-CT compared with contrast-enhanced CT alone. The accuracy of PET-CT was 86% compared with 68% for CT with all false-negative (n=3) and a false-positive occurring between four and eight weeks after treatment. Imaging eight weeks or more post-treatment resulted in the specificity of CT of 28% compared with 100% for FDG PET-CT. An example of a head and neck IMRT plan is shown in *Figure 3*.

Thoracic Tumors

For lung cancers, the presence of mediastinal involvement dramatically alters the outcome of these patients treated with unimodality or multimodality therapy. It is clear that PET and PET-CT has an excellent negative predicative value (87–100%) compared with surgical staging. The positive predictive value, however, remains less than optimal at <80%. Therefore, in patients with PET-negative studies of the mediastinum, mediastinal and/or elective nodal irradiation can be safely omitted. Others have shown that PET-CT is more accurate in predicting nodal stage than PET or CT alone in non-small cell lung cancer.[3] Elimination of elective nodal stations by effective prediction of involvement has enabled dose escalation programs such as reported by Ruysscher et al.[4] They were able to escalate therapeutic doses to 84 Gy before reaching dose-limiting toxicities necessitating study closure. More importantly, the treatment of lung cancer is often complicated by an associated infiltrate and/or atelectasis. In this setting, it is often quite difficult to distinguish these processes from the

Figure 3: Nasopharyngeal Cancer IMRT Plans Showing Dose Distribution on CT and PET



Note the high-dose region corresponding to the FDG-avid area.
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tumor itself. Consequently, the entire region is often incorrectly contoured as part of the planning target volume (PTV). The obvious consequence of this is the irradiation of relatively normal, though reactive, lung tissues in patients with already compromised pulmonary function. Schmuecking and colleagues have shown that PET-CT may substantially reduce the PTV by up to 22%, although in 10% of patients the PTV actually grew as a result of functional imaging.[5] Others have shown similar improvement in tumor volume definitions using PET-CT for non-small-cell lung cancer (NSCLC).[6]

For small-cell lung cancer, the use of PET-CT is less established. However, it appears that PET-CT will move a substantial proportion of patients to the next stage, thereby potentially altering their management.

In terms of predicting long-term survival, there is clear evidence that the change in FDG PET uptake can predict survival, leading to the conclusion that morphometric tumor response after treatment may strongly correlate with metabolic remission by PET.[7]

Gynecological Cancers

PET and PET-CT have been shown to be superior to CT alone in the staging of cervical cancer.[8,9] The detection of occult pelvic and para-aortic metastases using PET-CT has been used to select patients who might benefit from extended-field intensity-modulated radiation therapy (EF-IMRT).[10] Furthermore, at least one author has proposed dose escalation using EF-IMRT in locally advanced cervical cancer.[11] Although only a dosimetric study,using 2.4 Gy per fraction as an integrated boost to known para-aortic disease, the author's own institutional experience appears to indicate that such an approach is both clinically feasible and effective in sterilizing known disease without undue treatment-related toxicities. Chung et al. have shown that post-treatment FDG-PET surveillance in 121 patients was effective in detecting recurrence in 76 patients, 20 of whom were asymptomatic.[12] Other research groups have shown similar results.[13]

Avril et al. reported preliminary data of a small trial in patients with advanced ovarian cancer—stages three and four. That study evaluated the efficacy of functional imaging in neo-adjuvant chemotherapy. PET response after the first and second cycle of chemotherapy clearly predicted likelihood of survival with a median survival time of 38 months in responders and 23 months in non-responders.[14] Although radiation therapy is not routinely used for ovarian cancer, special indications may offer an opportunity for focal irradiation in patients who have completed consolidating chemotherapy after maximal surgical debulking. In these cases, focal residual masses or focal recurrences may be effectively managed with irradiation.

Brain Tumors

Contrast-enhanced CT and MRI remain the basis for the current practice of radiation treatment planning for brain tumors. Solberg and colleagues have

exploited FDG-PET for radiosurgery and IMRT using a simultaneous integrated boost (SIB). In that study, the margins of the tumor were treated at 1.8 Gy per fraction, whereas the PET-avid areas received 10–20% higher dose, without untoward toxicities. Additionally, early experience with O-(2-[18F]fluoroethyl)-L-tyrosine PET showed that this modality is useful in distinguishing recurrent tumor from treatment-related effects. Using the more conventional FDG-PET and PET-CT, others have shown that this modality is useful in differentiating tumor recurrence from radiation necrosis.[15]

Surveillance and Detection of Recurrence

The detection of recurrent disease is clearly a great opportunity for PET-CT. It is proposed that early detection of residual or recurrent disease may offer the opportunity for early salvage, which may alter the course of a variety of malignancies.

System Costs

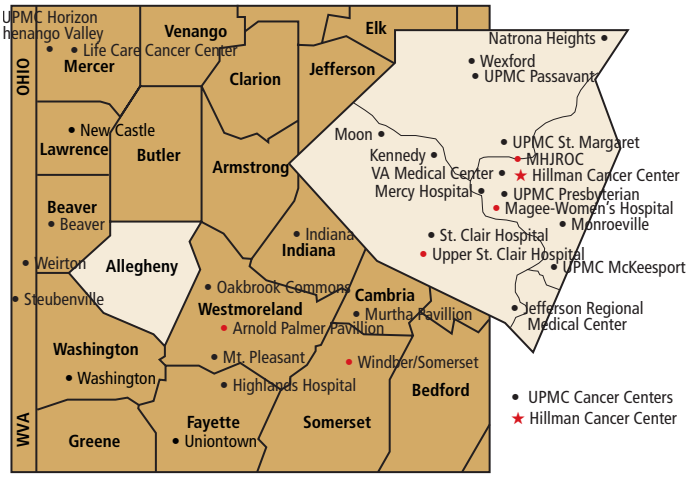
In the author's practice, PET-CT simulations are read as diagnostic studies while being simultaneously used for radiation treatment planning. This offers the best of both worlds and eliminates the need for a separate imaging study.

Cost per systems is approximately US$2.2 million, which includes the PET-CT, the carbon fiber flat table-top necessary for radiation treatment simulation, and in-room movable lasers, among other radiation-specific devices.

A Novel Implementation of PET-CT Simulation

Traditionally, high-end technologies, including imaging systems, have been relegated to tertiary-care hospitals and specialty facilities, thereby limiting accessibility of state-of-the-art care to the vast majority of cancer patients. If we are to continue to diminish the disparities in healthcare that now exist, novel solutions are necessary—particularly if we aim to continue increasing levels of quality and innovation in American oncological care. In Western Pennsylvania, the author and colleagues have constructed a unique model of PET-CT simulation for 21 geographically diverse cancer centers serving more than 40,000 new cancer patients each year. The University of Pittsburgh Cancer Institute and UPMC Cancer Centers' hub and spoke model offers a unique mix of an National Cancer Institute (NCI)-designated Cancer Center with a community cancer program delivery. The hub and spoke model (see *Figure 4*) recognizes the importance of bringing high-quality, evidence-based oncological practice and services to patients close to home. As a result of this configuration, we have formulated a mix of fixed PET-CT simulators with a mobile PET-CT simulation solution, which services the cancer centers in a 90-square mile radius. As a result, most patients need to travel only a few miles to receive diagnostically advanced imaging, radiation planning, and delivery services. This may be one of several models that can be used to lower the economic barrier to the implementation of state-of-the-art imaging and radiation delivery over a large geographical region.

Figure 4: UPMC Cancer Centers' 'Hub and Spoke' Model



Model allows for affordable PET-CT simulation via a combination of fixed and mobile solutions. Red location indicated fixed units.

Summary

Major advances in anatomical and functional imaging are revolutionizing the diagnosis, staging, and surveillance of cancer patients in the US. The accumulating evidence appears to show the importance of functional imaging, i.e. PET-CT, in radiation treatment planning and delivery. The convergence of key concepts of biological target volumes, accounting for anatomical and functional characteristics of malignancy, serve as the foundations upon which the next great leaps forward in cancer care using therapeutic irradiation will be based. ■

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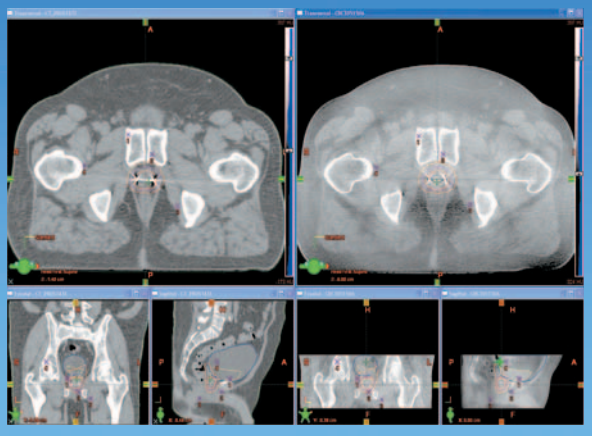
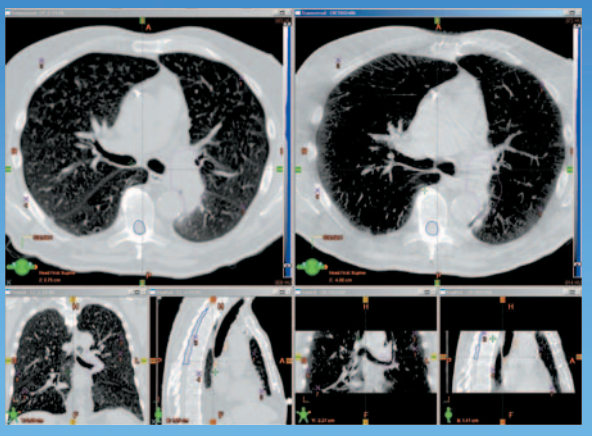
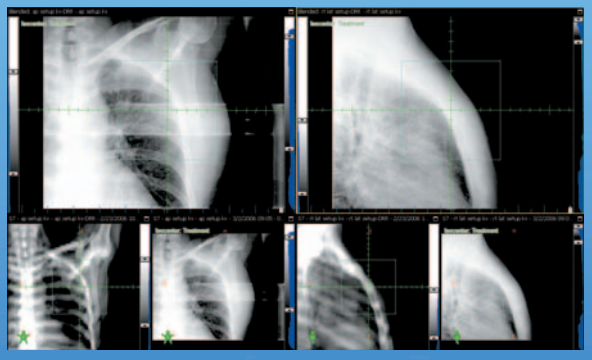
Imaging as unique as each patient



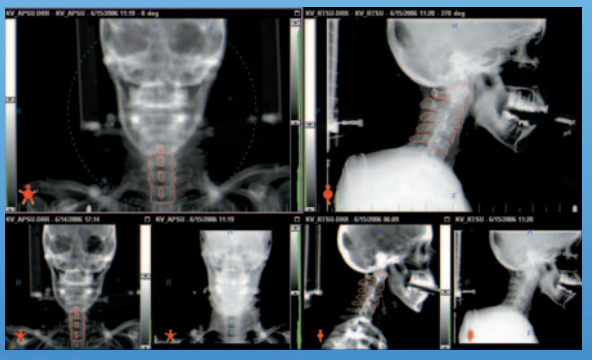
› *Cone-beam CT images of a prostate patient.*



› *Cone-beam CT images of a lung patient.*



› *Radiographs of a breast patient.*



› *Radiographs of a cervical spine patient.*

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