Chapter 17
Radiation Oncology

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Abstract

Radiation and surgical oncology share the common drive for localized intervention and minimal side-effects. These two disciplines are converging in their search for minimally invasive approaches to achieve this objective. New techniques have recently been developed to localize and characterize oncologic targets, and as target localization techniques and treatment approaches have become more precise, the planning and guidance tools for radiation oncology and surgical therapies have converged. Imaging also provides the opportunity to provide feedback relating to the progress of the treatment to the oncologist. This chapter discusses the nature of the cancer intervention philosophy, reviews technological advances in the use of imaging to guide radiation therapy, highlights the potential for fusion of therapies (i.e., surgery and radiation) through the use of image-guidance, and identifies trends for integration of image-guidance approaches in the community.

17.1 Introduction

Oncology is a rapidly evolving field with great promise for both existing and novel forms of localized cancer therapy. At the forefront of this evolution are the development of exquisite characterization of the target *in situ* and the adaptation of imaging technologies to the treatment context.

The advances in diagnostic imaging have increased the sensitivity and specificity for target detection and characterization, which has heightened the interest in conformal targeting of the disease tissues for reduced toxicity. It can be expected that the continued developments in diagnostic imaging will drive this dynamic with growing pressure in the development of minimally invasive approaches to intervention. This chapter reviews the mechanisms and trends for image guidance adoption in the community, after a brief introduction to the nature of the cancer intervention philosophy.

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17.2 Oncological Targets and the Nature of Disease Management

Successful treatment of localized cancer targets poses a complex and challenging problem. From earliest records, the disease is characterized by its remarkable invasive entanglement in the surrounding normal tissues. The desire to maintain function in the surrounding tissue is often compromised in exchange for confident eradication of the disease from its midst. The aggressive nature of cancer and its capacity to recur, given the slightest of residue, forces the clinician to take an approach of *confident eradication*. Compromising eradication in exchange for reduced toxicity is, in general, a temptation that is not to be taken lightly. More clearly, the concept of a partial intervention is not an approach that applies in such a disease where incomplete resection assures recurrence and leaves the patient with reduced capacity for further intervention.

The invasive nature of the disease has also evolved forms of therapy that can be safely applied under a range of presentations of the disease; from an isolated, accessible target to those intertwined with critical normal tissues. The two major forms of intervention are surgery and radiation therapy. Briefly, surgery involves tissue resection and radiation therapy involves irradiation of targets and normal tissues. The latter has the advantage of a preferential cyto-toxicity for cancerous cells relative to normal cells. These two therapies are applied in all varieties of localized cancer therapy and together often provide a complementing pair. No further description of these two interventions is required in this chapter; however, it is important to highlight the differences in the nature of their intervention, as it is relevant to the image guidance context and the ever-present tradeoff between eradication of the tumor and preservation of normal tissue.

In both surgical and radiation intervention, a simplistic but relevant description of the objective is to eliminate cancerous cells. In the surgical context, the cancer cells are physically resected with the removal of tissue. This resection could be considered as a binary intervention – either the cells were removed or not. In the radiation therapy context, each irradiation or fraction has some probability of inducing the death of a cell.

This probabilistic nature of the intervention provides a much more forgiving instrument when geometric uncertainties are present. Furthermore, it allows the therapy to preferentially target cancer cells relative to their normal cells, even when the two cell types are colocalized in space – a situation in which geometric selection of the cancer cells from the normal cells would require a level of precision and accuracy on the scale of a single cell. It is this *selective nature* of the radiation intervention that has made it so attractive to the oncologist, as it allows for some level of selection when geometry does not provide the opportunity. To maximize the potential of this selection process, however, the therapy needs to be broken into a number of

repetitive fractions; thereby allowing the differential cancerous cell kill to accumulate to a level of significance [Bernier et al. 2004].

Recent developments in image guidance have begun to shift this radiation therapy practice toward fewer fractions. In the case where the number of fractions is reduced to less than ten, it is referred to as hypofractionation, and often these few numbers of treatments are applied in a stereotactic approach [Leksell 1951]. The broad use of the stereotaxy label is somewhat historical and simply communicates the expectation that these treatments are delivered with a very high level of precision and accuracy, often through *calculated* coordinates of a target.

Recently, image-guided approaches, combined with hypofractionation, have been referred to stereotactic radiosurgery or SRS (in the cranium) and stereotactic body radiation therapy (SBRT). Using different fractionation schedules, radiation intervention has a nature of intervention that ranges from the selective to the ablative, where its mode of use is more akin to surgical intervention. It is of great relevance to this chapter to recognize that this remarkable transformation of radiation intervention was made possible by the development of image guidance methods that offer an appropriate level of precision and accuracy in the geometric targeting of the dose.

Development of more specific imaging techniques in the process of diagnosis will have a synergistic interaction with image guidance technology developments. Conventional radiation oncology practice has targeted the entire volume of the gross disease with uniform dose of a prescribed level. The identification of a subtarget that would represent elevated tumor burden or radiation resistant cells opens the opportunity to apply increased dose to this subregion. Such a dose-sculpting concept [Ling et al. 2000] is exciting, and is only feasible if methods can be developed for assuring the dose is delivered to this region, and not a surrounding normal structure. In this way, the advantages of improved target definition and the advancements in therapy targeting are both required if the full benefit of image-based target characterization is to be exploited for the benefit of the patient.

17.3 Imaging and Feedback in Intervention

17.3.1 Formalisms for Execution of Therapy

The development of image guidance in the context of radiation therapy has been substantially accelerated by the creation of a robust lexicon for communicating the intent of the therapeutic intervention, formalizing the description of the *prescription*. The International Commission of Radiological Units (ICRU) has provided a forum for the generation of standardized methods of prescribing radiation therapy [Measurements 1993, 1999].

The evolution of the ICRU Reports #50 and #62 over the past 20 years has been an important “structural breakthrough” in the development of

image guidance as it is currently practiced in radiation oncology. The documents created a nomenclature that allowed the dosimetric and geometric objectives of the radiation intervention to be communicated from the clinician to the rest of the treatment team. It also introduced a principle that is central to the image guidance task; geometric constructs or *margins* that explicitly accommodate the technical challenge of colocalizing the radiation dose distribution with respect to the tumor and normal tissues within the human body, over the many fractions of radiation treatment. The formalization of this margin concept has provided a fulcrum for the advancements of image guidance technologies by clarifying that component of the intervention is a by-product of imperfections or incapacity in the fidelity of the delivery scheme. The reduction of these margins has become a focus of the community, as they are directly associated with excess toxicity and, therefore, constraints on dose escalation of increased cure. Some of the elements of the ICRU formalism employed in radiation oncology are presented in (Fig. 17.1).

The volume of irradiation described by the planning target volume (PTV) can be contrasted against the supporting clinical target volume to illustrate the penalty associated with geometric uncertainties in the delivery of therapy. The methods employed to characterize uncertainty in the surgical context have been largely restricted to registration errors related to points in space employed for registration and for targeting [Fitzpatrick et al. 1998]. The development of a formalism in support of surgical intervention is an objective that would assist in the rational deployment of image guidance across the oncology field.

17.3.2 Dimensions of an Image-Guided Solution for Radiation Therapy

The selection or development of an appropriate image guidance solution is a complex process that typically contains compromises between clinical objecttive, availability of technology, efficiency, and manpower [Jaffray et al. 2005]. The simple development of an imaging method falls far short of the successful implementation of improved accuracy and precision in intervention. The following list identifies some of the many factors that must be considered in establishing an image guidance solution:

1. Clinical objective (targeting/normal tissue sparing)
2. Structures of interest (target/surrogates, normal structures)
3. Desired level of geometric precision and accuracy
4. Residual uncertainties to be managed (e.g., through the use of margins in RT)
5. Method of intervention (constraints, degrees of freedom)

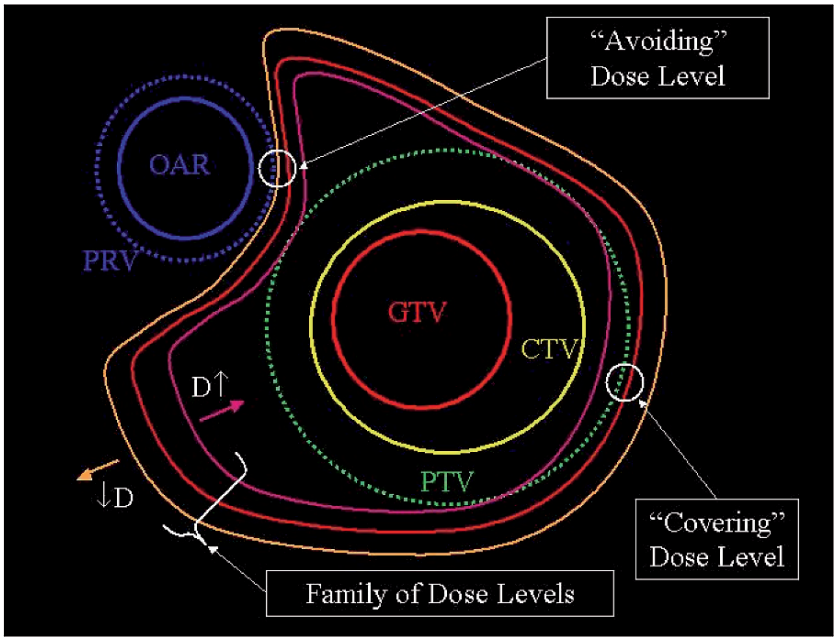

Fig. 17.1. An illustration of the ICRU constructs employed in the prescription and design of radiation therapy. The *gross tumour volume* (GTV) represents the component of the disease wherein imaging methods can be employed to characterize its three-dimensional morphology. The *clinical target volume* (CTV) accommodates the fact that clinical knowledge of the disease supports treating volumes that exceed the "imageable" volume based upon suspicion of microscopic disease extension into the surrounding tissues. It is often the case that GTV and CTV volumes will be prescribed different dose levels (although not reflected in this illustration). In addition to the target volumes, organs at risk (OAR) constrain the placement of dose. These structures are critical to function and have a sensitivity to the radiation. The dotted volumes (*planning target volume* or PTV and *planning risk volume* or PRV) are constructs employed in the design of the therapy. These constructs are generated specifically to accommodate the geometric targeting uncertainties of radiation delivery process. As "volumes" they do not reflect any specific tissues, nor are they related to any volume within the patient. Their purpose is to represent the geometric inaccuracy and imprecision in overall process. The margins between CTV and PTV (or OAR and PRV) are sometimes referred to as "safety margins," as they assure cover and avoidance of the various anatomical volumes. A simple dose distribution has been overlaid (i.e., Family of Dose Levels) to illustrate the selection of the "red" dose level for coverage of the PTV volume and the verification that the "orange" dose level does not reach the OAR. The determination of appropriate safety margins is a challenging element of radiation therapy and it requires an understanding of the sensitivity of the structure to dose variation, the magnitude of the dose gradient at that location, and prior knowledge of the geometric uncertainties in actual CTV and OAR locations over the course of therapy. Typically, this information is generated for a population of patients and a specific treatment technique

6. Gradients in the intervention (dose, ablation)
7. Strength of surrounding surrogates (bone, skin)
8. Consideration of implanted markers as surrogates of target/normal structure
9. The length of the procedure of number of fractions for which guidance is required
10. Available treatment capacity (treatments/hour) on treatment system
11. Application for all or some patients
12. Identification of individuals responsible for development
13. Identification of individuals responsible for commissioning and performance characterization
14. Identification of individuals responsible for performing quality assurance on the system and periodic verification of performance
15. Development of a structure for delegation of responsibility with respect to measurement, analysis, decision, and operation.

These factors highlight the scope of the problem, with issues reaching into the domains of clinical operations, training of staff, and delegation of responsibility. The development of clinical image guidance solutions in oncology practice requires a very broad investment by a number of groups and disciplines. Experience in radiation oncology has demonstrated that effective deployment has even required the development of education programs to bring all the disciplines into the process and to clarify the relative roles these disciplines play in the image guidance paradigm. It is likely that similar investments will be necessary in the surgical context if these advances are to become efficient and broadly applied.

17.3.3 Image Guidance Technologies in Radiation Oncology

The localized nature of the intervention in radiation therapy clearly requires some level of targeting or guidance. Conventional approaches have largely relied on the use of external skin marks for the routine positioning of patients for radiation delivery. Typically, a patient will be imaged using either radiographic or CT methods to determine the location of internal targets. During this process, external reference marks are drawn or tattooed onto the patient's skin. In addition to these marks, anatomical reference points (e.g., sternal notch, scar, umbilicus) will also be documented to reinforce the marks over the course of delivery.

Once the treatment plan is complete, the patient will be positioned for their daily treatment using these reference marks by aligning them to a set of orthogonal lasers located in the treatment room. The lasers beams (typically 5–7) are refracted to generate planes that all intersect at the

isocenter of the treatment machine with a tolerance of better than 2 mm [Kutcher et al. 1994]. This isocentre is the point in space at which all treatment beams intersect regardless of the angle of the gantry or couch. It has long been understood that the use of skin-based surrogates for internal target positioning introduces significant geometric inaccuracies in the placement of dose within the body, but imaging methods to resolve this have been slow (decades) in development.

The past 20 years have seen steady improvements in this regard with initial efforts focused on the development of "portal imaging," that is, the use of the radiographic properties of the treatment beam to visualize the internal anatomy and, more recently, a variety of volumetric imaging technologies used in addition to portal imaging to improve visualization and allow 3D assessment of target and normal tissues (Fig. 17.2).

The past 15 years have seen dramatic advances in portal imaging technology. The introduction of the Kodak ECL film system and the development of computed radiography (CR) systems have improved the quality of the images produced with these systems. Munro [1999] provides an excellent review of electronic portal imaging devices in the clinical setting and identifies the current status of the commercially available devices. The quality of images generated with these new devices is satisfactory at clinically acceptable imaging doses (2–8 cGy) and has sufficiently large field-of-view to cover most clinical fields. The images formed with these systems can not only guide the treatment, but can also verify the shape and orientation of the treatment field [Schewe et al. 1998].

Visualizing surrogates of target position and the edge of the treatment field in the same image has made the portal imaging approach extremely robust and relatively easy to integrate into clinical practice. Portal filming can be used as a robust source of data for off-line correction schemes and many of the early feasibility studies on the implementation of off-line correction strategies were tested on portal film based measurements. Electronic portal imaging devices (EPIDs) have spurred the development of online repositioning strategies, as well as provided a wealth of data for support of off-line approaches. The continued development of portal imaging technologies will drive reduced imaging doses and permit more frequent imaging in support of both online and off-line strategies. These technological advances will provide robust systems for monitoring the quality of therapy. However, the inherently low subject contrast in the MV radiographs and restriction associated with imaging through the treatment port has been spurring the development of kilovoltage (kV) imaging systems on the medical linear accelerator. The future of guidance and verification in radiation therapy will most likely be a hybrid of MV and kV technologies.

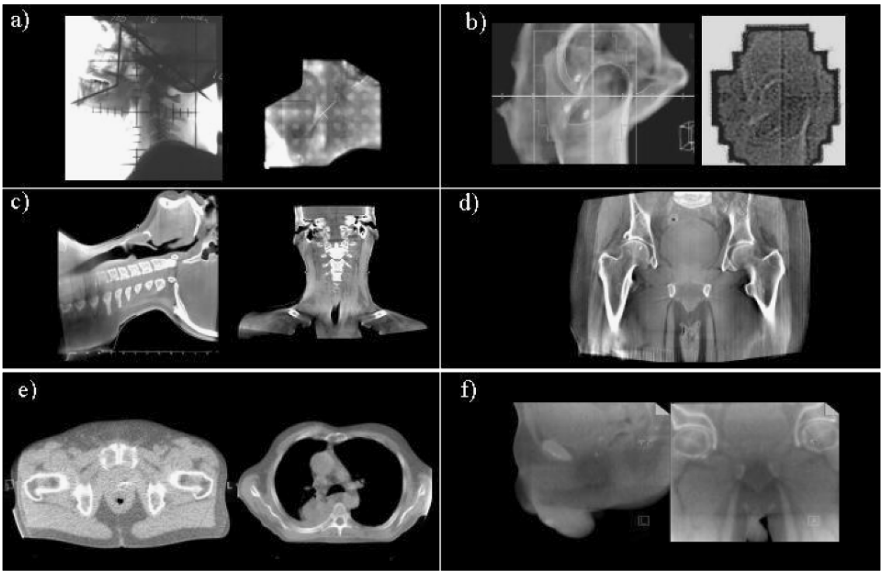

Fig. 17.2. Image guidance methods employed in radiation oncology practice generate a variety of image types. (**a**) Radiographic design of treatment fields using kV radiographs acquired in the planning stages were verified at the time of treatment using portal images. These images were generated with the actual treatment port and provided detection of bony anatomy and air passages. Often the images were reduced in quality by the interference of the treatment table, or trays used to hold the field-shaping blocks in place. (**b**) The development of electronic portal imaging systems allowed images to be detected at the time of treatment and adjustments in patient position could be made before each fraction. This online approach, combined with the implantation of markers, has become a very common method of achieving accurate and precise targeting of the prostate gland. The two images in frame (**b**) would be compared each day to estimate the necessary adjustment to the patient's position. (**c**, **d**) kV volumetric cone-beam CT images acquired on the treatment unit provides soft-tissue visualization without the use of implanted fiducials. The head and neck images shown in (**c**) can be compared with the portal images of the head and neck in the frame directly above. Similarly, the prostate dataset in frame (**d**) can be contrasted with the visualization of prostatic anatomy in the portal image on the right of frame (**b**). Soft-tissue imaging with the megavoltage treatment beam has been progressing well. MV CT from the Tomotherapy platform are shown in frame (**e**) and MV cone-beam CT images from the Siemens MVision system are shown in frame (**f**)

17.3.3.1 Kilovoltage Radiography and Fluoroscopy for Bone and Implanted Surrogates

There have been many embodiments of kV radiography and/or fluoroscopy integrated with the radiation therapy treatment device [Shirato et al. 2000]. Figure 17.3 illustrates direct integration of kV X-ray sources as proposed by multiple investigators. Others have proposed attaching a kV X-ray tube to

the gantry and achieving MV and kV source coincidence by a gantry rotation or table translation [Biggs et al. 1985; Drake et al. 2000]. Developments have also proceeded in the construction of room-based kV imaging systems [Raaymakers et al. 2004]. Both approaches are designed to localize the bony anatomy or surrogate structures (markers, etc.) through acquisition of at least two radiographs that are acquired at two distinct and known angles. In the gantry-based approach, a single imaging system is used in conjunction with the gantry rotation to generate the necessary images. Room-based systems typically include a minimum of two complete imaging systems (source and detector) and have been constructed with up to four separate systems. Kurimaya et al. [2003] use four systems to permit continuous stereo monitoring regardless of linear accelerator gantry angle. The types of detectors used in these systems range from conventional radiographic film, to image-intensifiers, to charge-coupled devices/phosphor screen-based systems, to large-area flat-panel detectors. The continued development of large-area, high-performance flat-panel detector technology can be expected to spur this approach in coming years. This is clearly demonstrated in the rapid dissemination of the Elekta Synergy System, the BrainLab Novalis unit, and Varian's OBI Systems as illustrated in Fig. 17.3.

17.3.3.2 Kilovoltage Computed Tomography (kVCT)

Dedicated radiographic imaging systems promise to revolutionize radiation therapy practice by increasing the precision with which the patient's bony anatomy can be positioned with respect to the treatment beam. These systems can also be extended to more mobile targets by implantation of fiducial markers directly in the targeted structures. The generality of this approach is limited, as it does not support visualization of adjacent dose-limiting normal structures. The advancement of a general solution for precision radiation therapy throughout the human body requires the capacity to visualize soft-tissue structures in the treatment context. There have been a number of volumetric imaging modalities proposed for this task, including, ultrasound (US) [Kurimaya et al. 2003], computed tomography (CT) [Court et al. 2003], and magnetic resonance (MR) imaging [Raaymakers et al. 2004].

17.3.3.3 Conventional CT in the Treatment Room

The placement of a conventional CT scanner in the treatment room with a known geometric relationship with respect to the treatment machine offers a feasible and robust approach to implementing CT-guided radiation therapy. Uematsu et al. have been developing this approach over the past 7 years [Simpson et al. 1982].

Currently, multiple manufacturers provide products of this type (e.g., Siemens' Primatom; Mitsubishi's accelerator in combination with a General

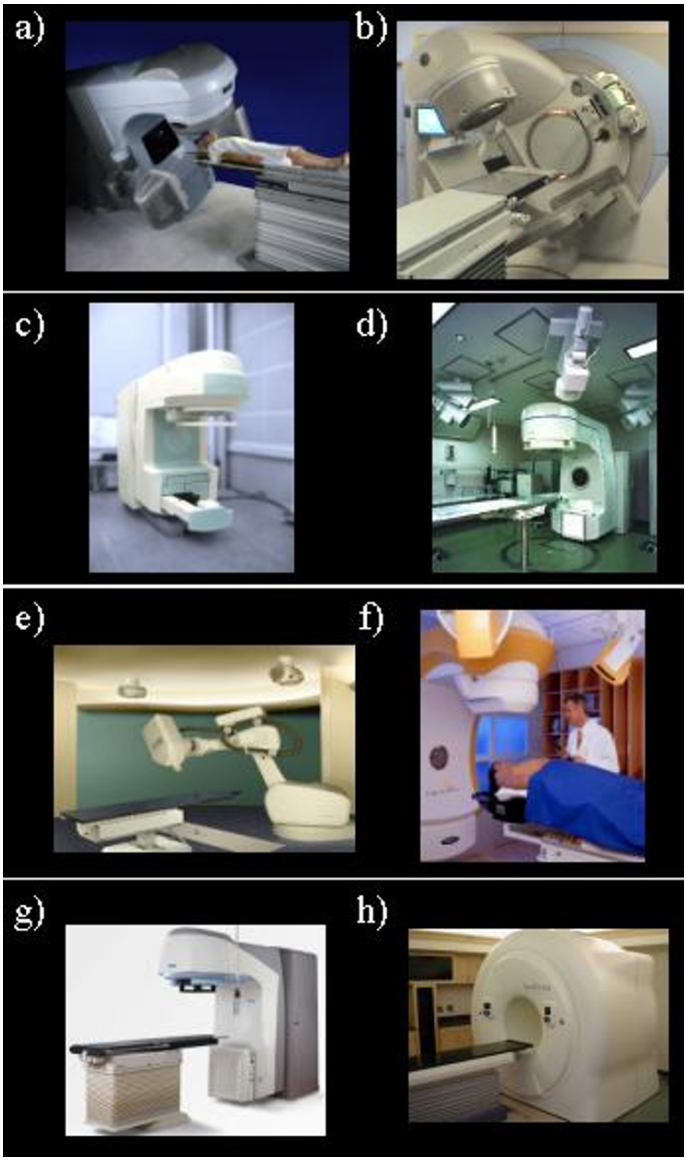

Fig. 17.3. There are numerous forms of image guidance capable treatment machines. The addition of kilovoltage (kV) imaging systems to radiation therapy treatment units has become commonplace. Typically, these systems either integrate the kV system on to the gantry for radiography and cone-beam computed tomography (CBCT) [(**a**) Elekta Synergy, (**b**) Varian Trilogy, (**c**) Siemens Artiste] or employ room-mounted radiographic systems [(**d**) Shirato et al., (**e**) Brainlab Novalis, (**f**) Accuray Cyberknife). Solutions that generate soft-tissue images of the patient using the treatment (MV) beam have also been developed [(**g**) Tomotherapy, (**h**) Siemens MVision]

Electric CT scanner, and Varian's ExaCT targeting system) [Brahme et al. 1987]. All systems are based upon a CT scanner placed in close proximity to the medical linear accelerator, allowing a single couch to be moved from an imaging position to the treatment position. These systems vary in the amount of motion and degrees of freedom required to move the patient from one position to the other. The commercially available systems minimize the amount of couch movement by translating the CT scanner gantry during acquisition. This has the perceived merit of avoiding differences in couch deflection at different couch extensions [Nakagawa et al. 2000].

While the installation of a second costly system in the treatment room is perceived to be somewhat inelegant, it has a clear advantage in that it leverages all the development that has been invested in conventional CT technology over the past 20 years, leading to unquestioned image quality and clinical robustness. Forrest et al. [2004] report a positional accuracy for the Mitsubishi-based system of under 0.5 mm, while Court et al. report an accuracy of 0.7 mm that can be reduced to 0.4 mm when using radio-opaque fiducial markers [Mosleh-Shirazi et al. 1998]. Such accuracy, in combination with excellent image quality, promises excellent management of interfraction setup errors and organ-motion. The issues of motion between imaging and delivery remain and needs to be accommodated through the appropriate selection of PTV margins.

17.3.3.4 Cone-Beam CT on the Medical Linear Accelerator

An alternative approach for CT-based image guidance is to integrate the CT imaging system directly into the mechanics of the medical linear accelerator, providing an integrated approach that echoes the objectives of Uematsu's device. Current medical linear accelerators are limited to approximately 360° of gantry rotation. This would limit a conventional CT approach on such a gantry to one slice per revolution. The IEC limits on gantry rotation rate (~1 rpm) would make imaging with such a platform prohibitive.

Recent advances in large area flat-panel detector technology offer the opportunity to implement cone-beam computed tomography [Groh et al. 2002], permitting a volumetric image to be acquired in a single revolution of the gantry structure. Pouliot et al. [2005] have been exploring this approach over the past 10 years. Figure 17.3 contains a photograph of the cone-beam CT systems offered by Elekta, Varian, and Siemens.

Advantages of such an approach are numerous, provided cone-beam CT image quality is sufficient to visualize soft-tissue structures of interest in the treatment context. This has been examined through numerous investigations [Lattanzi et al. 1998] and current flat-panel technology appears to provide a reasonable level of performance with continued performance enhancements anticipated. The cone-beam CT approach provides volumetric imaging in the treatment position and allows radiographic or fluoroscopic

monitoring throughout the treatment procedure. Clinical images generated on the Elekta Synergy system are shown in Fig. 17.2. These images illustrate the system's capacity to visualize soft-tissue structures with substantial detail in all three spatial dimensions. The dose delivered in the imaging process was less than 3 cGy. An integrated imaging system with this level of spatial resolution and soft-tissue visualization capability has a significant potential to alter radiation therapy practice.

17.3.3.5 Megavoltage Computed Tomography (MVCT)

The need for accurate electron density estimates for treatment planning was the initial rationale for developing MVCT imaging systems and their use for patient and target structure localization was secondary. A number of investigators have been exploring the use of MV beams in CT imaging over the past 20 years [Molloy et al. 2004].

The Slice-Based Megavoltage CT

The initial development of a MV CT scanner for radiation therapy is attributed to Simpson et al. [Raaymakers et al. 2004]. Their approach was based upon a 4 mV beam and a single linear array of detectors. Brahme et al. proposed employing a 50 mV treatment beam for CT imaging in 1987 [Mageras 2005]. In their proposal, the high-energy beam would create contrasts comparable to a 300 keV due to the dependence of the pair production X-ray interaction process on atomic number.

Bijhold et al. [1992] were the first group to have reported clinical experience based upon MV CT images, using their single-slice system to treat 15 patients for metastatic and primary lung cancer. In this system, a single linear detector consisting of 75 cadmium tungstate crystals is mounted on the accelerator gantry and can be readily removed. The authors indicate that a spatial resolution of 0.5 mm and contrast resolution of 5% can be resolved with the system. Clinical imaging doses of 2.8 cGy were delivered during patient imaging and sample images are shown in Fig. 17.2. The most recent exploration of MV CT imaging has been in the development of the Tomotherapy™ treatment platform [Van Herk 2004].

MV Cone-Beam CT on the Medical Linear Accelerator

Limitations in gantry rotation have also spurred the development of cone-beam MV CT on a medical linear accelerator. With the exception of Mosleh-Shirazi et al. [Yan et al. 2005], these developments have come as a by-product of advances in commercial portal imaging technology. Groh et al. [Balter and Kessler 2007] have reported on the challenges associated with achieving high signal-to-noise performance at MV energies with low-efficiency flat-panel detector technology. Despite the low efficiency of these systems, the visibility of high contrast structures, such as air and

bone, should be reasonable at clinically acceptable doses (~5 cGy). These systems have matured and are becoming commercially available [Kong et al. 2005]. Images acquired with such a system are shown in Fig. 17.2.

17.3.3.6 Ultrasound Approaches in IGRT

The US approach had been proposed for many years [Kong et al. 2006] and became commercially available in the late 1990s with the introduction of the BAT™ system by Nomos Corporation [Blomgren et al. 1995]. Ultrasound has many features that make it a technology well-suited for IGRT applications. It is low-cost, volumetric, has no known side-effects, is interactive in its use, and provides soft-tissue contrast that can challenge more expensive modalities such as CT or MR.

As in any technology, its strengths are also its weaknesses. The contrast-inducing reflections limit the depth of targets to which the modality has been applied and the need for acoustic coupling requires robust physical contact between the probe and the patient's external contour. The ultrasound images are formatted in 3D using an US probe position sensor (either mechanical or optical) and visualization software. The coordinate system of the resulting 3D US dataset is located in treatment reference frame and can be registered to the planning CT dataset through alignment with contours from the planning process. The discrepancy after alignment reflects the appropriate correction to be applied to patient position. The potential of disturbing the target location during imaging has been an area of investigation [Timmerman et al. 2005]. More recent studies provide an excellent review of the relative performance of US-based approaches in targeting of the prostate gland [Purdie et al. 2007]. The low-cost of the technology, its ease of integration, and its ability for real-time monitoring of soft-tissue structures suggest that this technology has a future in radiation therapy for both planning [Keall et al. 2006] and localization.

17.3.3.7 Developments in MR-Guided Radiation Therapy

The high contrast and noninvasive nature of magnetic resonance (MR) imaging has prompted the development of MR-guided radiation therapy systems [Purdie et al. 2006]. These systems seek to exploit the remarkable gains in MR engineering (in particular active shielding) made over the past several years to allow integration of the significant electromechanical elements of a medical linear accelerator into the treatment room. Alternatively, the use of Cobalt-60 sources has been suggested to further reduce the technical challenges.

The merits of these systems are arguably their ability to produce images of the internal anatomy during radiation delivery, and without additional imaging dose associated with X-ray based approaches. The selection of higher field systems would even offer benefits for improved identification

of targets at the time of treatment or assessment of therapy induced biological changes. To date, no MR-guided systems have been constructed; however, it is likely that prototypes will be available in the next few years.

17.4 Image-Guided Applications in Radiation Oncology

The growth of image guidance technologies have allowed new treatment approaches to be developed, and existing treatment methods to adopt image-guided approaches. In the following section, methods of oncology intervention that rely on image guidance approaches in the treatment context are described. The intention is not to provide a comprehensive description of these applications, but rather highlight a number of interesting models.

The past 5 years have seen a dramatic increase in the use of formalized, quantitative image guidance approaches in routine radiation therapy practice [Vicini et al. 2005]. While the technologies can be readily applied to various clinical problems, it is most informative to highlight specific clinical applications and comment on the clinical rationale. It is important to note that the advances in image guidance in radiation therapy have been made possible by substantial advances in 3D planning software and the availability of state-of-the-art imaging in the characterization of the target and normal tissues.

17.4.1 Prostate Cancer: Off-Line and Online Models

The past 10 years have seen a sharp increase in image guidance approaches being applied to radiation therapy of prostate cancer. This effort has been part of the broad initiative of dose escalation for increased probability of cure. The dose to the prostate has gone from 66 Gy delivered to simple, nonconformal volumes, to over 80 Gy with highly conformal approaches based upon methods that modulate the intensity of the treatment beam. This dose escalation has heightened the concerns regarding the volume of normal tissues irradiated with particular concern for the dose delivered to the rectal wall. The implementation of image guidance approaches allows confident reduction of the PTV margins and thereby reduction in the volume of normal tissue receiving the therapeutic dose level [Baglan et al. 2003].

Portal imaging approaches allowed bony anatomy to be localized on a routine basis with corrections for systematic errors in treatment setup [White in press; White et al. 2007]. However, the motion of the prostate gland relative to boney anatomy [Islam et al. 2006] is now a recognized and well-documented factor determining the size of the PTV margin [Pisters et al. 2007].

Schemes to accommodate the systematic errors in gland location relative to bony anatomy have been matured using off-line repeat CT imaging with excellent success [Ward et al. 2004]. An alternative to the off-line approach is to image every day and correct for any variations in prostate

location by adjustments to the treatment couch. This approach requires visualization of the prostate gland or reasonable soft-tissue surrogate. Such approaches have been effected in many institutions using portal imaging in combination with implanted fiducial (typically gold) markers within the gland prior to the start of therapy [Davis et al. 2005].

This approach allows fairly straightforward interpretation of the marker location and appropriate adjustment in patient position through simple couch translations. Often these approaches are deployed with threshold for adjustment (e.g., no corrections for displacements less than 3 mm) to minimize the number of adjustments, and prevent interventions that are less than the precision of the adjustment. Developments in soft-tissue imaging in the treatment room (e.g., cone-beam CT, Tomotherapy megavoltage CT, and ultrasound) are allowing the soft-tissue anatomy to be targeted directly without the need for fiducials. These approaches have been receiving mixed reviews and there continue to be concerns with regard to consistency of interpretation [Griffin et al. 2007].

Despite these concerns, it can be concluded that growth in the use of these approaches will continue as image quality and confidence in interpretation improves. The merits of soft-tissue guidance approaches include the absence of fiducial placement and the opportunity to track the dose accumulation in surrounding normal tissues. A major challenge in the use of soft-tissue guidance is in the determination of the appropriate intervention under conditions of target or normal tissue deformation. This is currently an area of research and development within the radiation therapy community [O'Sullivan 2007].

17.4.2 Stereotactic Body Radiation Therapy (SBRT) for Cancer of the Lung

Radiation therapy of cancerous lesions in the lung has demonstrated poor outcomes and driven the pursuit of dose escalation. Recent studies are demonstrating the potential clinical gains associated with increasing the applied dose [Bilsky 2005]. However, concerns regarding toxicity continue to constrain dose escalation [Bilsky 2005]. The dependence of lung toxicity on dose and volume makes the lung a clinical site for which increased precision and accuracy would offer further pursuit of dose escalation provided toxicity is limited. However, the technical challenges associated with maintaining high precision and accuracy over the multiple fractions (20+) of conventional dose regimen (~2 Gy/Fx) is forbidding. The past several years have seen significant interest and success in the treatment of early stage lung cancer using stereotactic methods.

As the name implies, the targeting of the radiation dose to the lesion is achieved through 3D localization at the time of treatment. Early pioneers in this approach, such as Kim et al., [2001] have employed a body frame to provide Cartesian referencing of the target within the body

at the time of treatment. This frame is to be replaced for each of the few (1–4) fractions delivered. This low number of fractions is the basis for the "hypo"-fractionation label.

Similar hypo-fractionated approaches were developed in Japan during the late 1990s [Siewerdsen et al. 2005] demonstrating the feasibility of these methods using image guidance. The past 5 years have seen maturation of clinical evidence to support these approaches both in terms of benefit and feasibility of applying this approach in the broader community [Wright et al. 2006; Yenice et al. 2003]. The recent completion of the RTOG #0236 clinical trial represented the first multiinstitutional trial of this kind in the North American setting (3 fractions at 20 Gy/Fx). Letourneau et al. [2007] have reported on the employment of cone-beam CT methods in the targeting of these lesions and highlighted inaccuracies in targeting based on boney anatomy alone.

The development of 4D CT methods (Fig. 17.4**)** have allowed characterization of the respiration-induced movement of these targets in 3D [Ekelman 1988]. This allows development of patient-specific motion profiles and corresponding planning target volumes [Gospodarowicz and O'Sullivan 2003], as well as the development of tracking and gating methodologies [Siker et al. 2006]. The use of SBRT in the lung is likely to increase dramatically over the next few years, given the clinical outcomes and the development of image-guided delivery solutions that are capable of assuring target coverage.

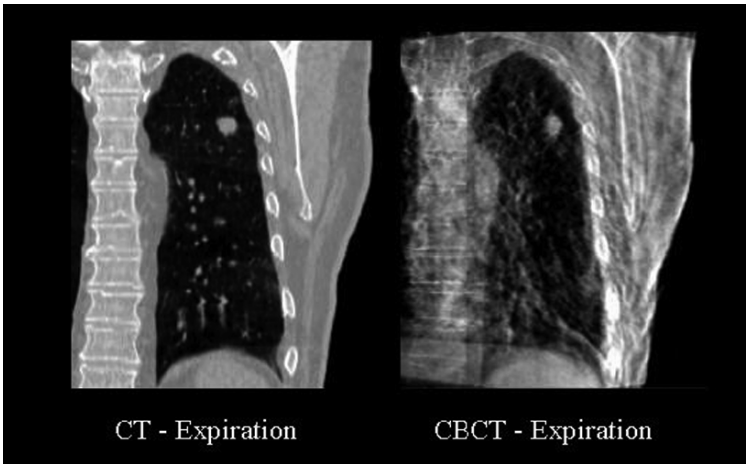

Fig. 17.4. Cone-beam CT guided radiation therapy of lung targets allows soft tissue targeting at the time of treatment. The image on the left illustrates the visibility of the lesion on conventional 4D CT imaging (expiration phase). The image on the right is the same breathing phase, but acquired at the time of treatment using 4D cone-beam CT. The use of images such as these for online guidance is becoming more commonplace

17.4.3 Accelerated Partial Breast Irradiation

The treatment of post-lumpectomy breast cancer has traditionally included uniform coverage of the entire breast and chest wall, as well as a small portion of the underlying lung [Lee et al. 2006]. Recent developments in technological capacity have raised the potential to reduce the volume of irradiation in a selected subset of patients, and furthermore, the fractionation schedule is modified. The rationale for these changes includes convenience, cosmesis, reduced toxicity in surrounding structures, and radiobiological arguments of equivalent control. For example, patients would receive 38.5 Gy in 3.85 Gy/fraction delivered twice daily for 5 consecutive days. The clinical target volume includes the lumpectomy cavity, plus a 10–15 mm margin bounded by 5 mm within the skin surface and the lung–chest wall interface. The planning target volume (PTV) included the clinical target volume plus a 10 mm margin [Von Hippel et al. 1999]. The technical studies to support this level of conformality are maturing. Rosenberg [1999] has reported on the suitability of 10 mm margins in covering the target volume.

In this technique, conventional clinical setup is employed using evaluations performed using portal imaging techniques. These studies examined the mobility of surgical clips relative to bony anatomy to gain confidence in the portal imaging-based assessments. Recent developments in cone-beam CT have allowed evaluation of seroma coverage directly [Nusslin 1995]. This study found that conventional skin mark positioning was able to achieve reasonable levels of targeting accuracy (2–3 mm standard deviation in the mean in the population) and precision (2–3 mm standard deviation in an individual) over the 1 week course of therapy. For the application of online corrections, an action level for correction of errors of 3 mm was demonstrated to be appropriate with more stringent levels producing no further improvements in precision or accuracy.

Overall, these investigations demonstrated that skin-based positioning produced acceptable levels of precision and accuracy for the PTV margins employed (10 mm). The additional benefit of the method may be in the reduction of these volumes, or in the assessment of seroma coverage at the onset of therapy as part of the overall assurance of treatment quality. It should be noted that the imaging doses delivered in these studies are small; however, the benefits of improved geometric targeting needs to be evaluated with respect to the potential risks associated with increased imaging dose to the contralateral breast.

17.5 Image Guidance Approaches that Bridge Therapeutic Modalities

Image guidance approaches are developing across the many forms of oncology intervention with remarkably similar issues and solutions. These

approaches share common issues of achieving precision and accuracy in the intervention for the purpose of limiting toxicity while assuring the success of the procedure. If the image-guided approaches are broadly successful, oncology intervention will become a carefully contemplated and meticulously executed series of interventions for the benefit of the patient. This type of execution opens the opportunity for the community to consider a much more coordinated form of cancer care that bridges the disciplines and binds them by the accurate record of intervention performed by their complementary discipline. The evolution of these steps will lead to the creation of intervention planning systems that bridge chemical, cellular, surgical, and radiation-based interventions.

17.5.1 The Optimal Intervention

In the following section, oncology treatment solutions that adopt a combined modality therapy approach with a dependence on image-guided methods are highlighted. The feasibility of these approaches is dependent on the elevated level of precision and accuracy that can be achieved with image guidance.

17.5.1.1 Preoperative Radiation Therapy in the Management of Sarcoma

The management of soft-tissue sarcoma (STS) is a rapidly evolving complex multidis-ciplinary activity. Recent studies have demonstrated the benefits for optimal combination of radiation therapy and surgery in some forms of STS. These investigations have demonstrated that the combination of preoperative radiation therapy followed by surgery permitted improved outcomes, with a penalty of post-surgical wound-healing complication. These observations raised the potential for a more conformal preoperative radiation intervention to minimize damage to normal structures that are supportive of the post-surgical recovery. To this end, a collaboration of surgeons, radiation oncologists, physicists, and therapists have implemented a novel practice for the management of STS that exploit all the elements of modern radiation and surgery (see Fig. 17.5). This approach hinges on a set of assertions:

1. The anatomy critical to wound healing can be identified and segmented prior to radiation therapy
2. The precision of therapy delivery allows minimal “safety margins” in the expansion of the CTV to the PTV
3. The planning process can employ intensity modulated radiation fields to conform the dose to these volumes while simultaneously avoiding the avoidance structures

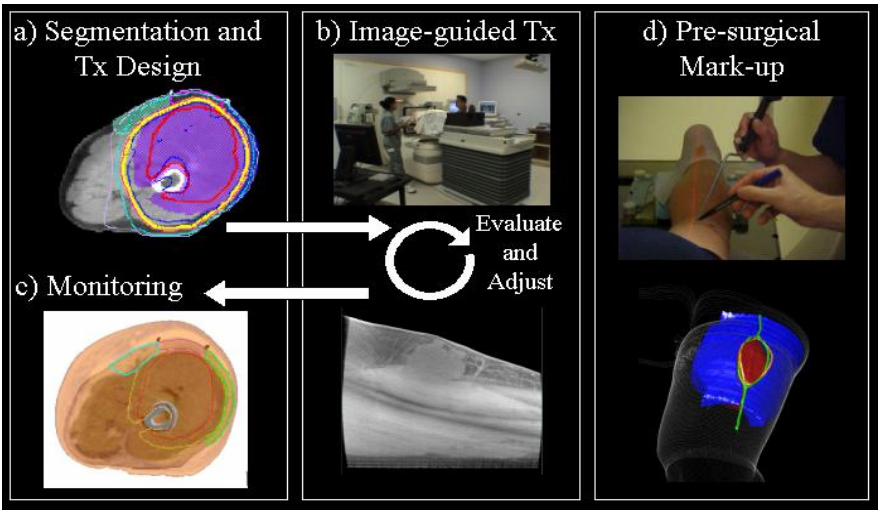

Fig. 17.5. The treatment of patients with soft-tissue sarcomas at Princess Margaret Hospital (Toronto, Ontario, Canada) is a multidisciplinary effort with involvement of surgeons, radiation oncologists, therapists, and physicists. (**a**) Disease and normal structures are identified and include volumes of interest in post-surgical wound healing as well as more conventional targets. Avoidance is only feasible if therapy is delivered with sufficient precision and accuracy. (**b**) Online image guidance using cone-beam CT allows assurance of targeting performance while also monitoring the juxtaposition of normal and disease structures over the course of therapy. Following radiation therapy, the regions of elevated dose are marked on the patient prior to surgery using a cross-calibrated optical tracking tool and the dose map used in the treatment design. Future versions of this model will include accurate dose tracking over the course of therapy

4. The surgeon can have knowledge of the regions of applied radiation dose at the time of surgery to appropriately include the viable tissues for postresection wound closure

Each of these steps draws on the latest in technologies to make them possible so that:

1. Target and normal tissues are identified by surgeons and radiation oncologists on multi-modal (CT and MR) datasets
2. Inverse planning methods are employed to design the intensity modulated radiation fields
3. Daily online guidance using cone-beam CT assures target coverage and normal tissue avoidance
4. Preoperative planning using an optical navigation system is employed to map the high dose regions to the skin surface immediately prior to surgical intervention

To date, this has been applied in a population of patients (>20) treated in the sarcoma program at Princess Margaret Hospital, Toronto, Canada.

17.5.1.2 Post-Surgical Radiation Therapy of the Spine

It is estimated that between 5% and 10% of all cancer patients will develop metastatic spinal tumors. Metastasis of cancer to the spine is characterized by both loss in structural integrity of the involved vertebrae and significant pain. The use of radiation therapy in combination with surgical stabilization of the vertebrae is growing in practice.

The developments of MR imaging for characterization of these lesions have allowed optimization of the therapy intervention depending on various parameters. Bilsky [2005] describes a decision-making framework for appropriate combination of surgery and radiation depending on many factors, including mechanical stability and radiation sensitivity (e.g., radiation sensitive lymphoma primary vs. radiation resistant renal cell primary). The surgical techniques applied in these procedures have undergone advancements with the maturation of pedicle screws and the use of polymethyl methacrylate (PMMA) for stabilization of the vertebral body. Image guidance methods have been proposed in these procedures to increase the accuracy of screw placement. These methods use preoperative images in the design of the pedicle placement, and efforts to introduce intraoperative imaging in spine surgery are making progress. Siewerdsen et al. [2005] demonstrated the use of intraoperative cone-beam CT systems for placement of pedicle screws in an application of photodynamic therapy in the treatment of mock metastases in a porcine model.

The application of radiation therapy in the treatment of spinal lesions is dominated by the radiation sensitivity of the spinal cord itself. Conventional radiation therapy used for pain management would irradiate the entire region, lesion, and cord to approximately 30 Gy. If radiation dose to the cord is taken beyond an average 45 Gy or sub-volumes in excess of 50 Gy, radiation myelopathy is likely to develop. These dose thresholds prevented retreatment or even aggressive treatment to adjacent lesions due to the concern of overlap. Image guidance approaches are now allowing cord-avoiding treatments to be applied with confidence and allowing aggressive retreatments to the same or adjacent regions. This technique is illustrated in Fig. 17.6. Recent developments in image guidance technologies may allow these treatments to be delivered in a single fraction that is designed at the treatment unit.

17.6 Opportunities in Image-Guided Therapy: New Information Driving Invention

The growing use of image guidance is evident across all the modalities of cancer management. From the perspective developed over years of involvement of image guidance technologies and processes, there appear to be two important dynamics that will advance these approaches further:

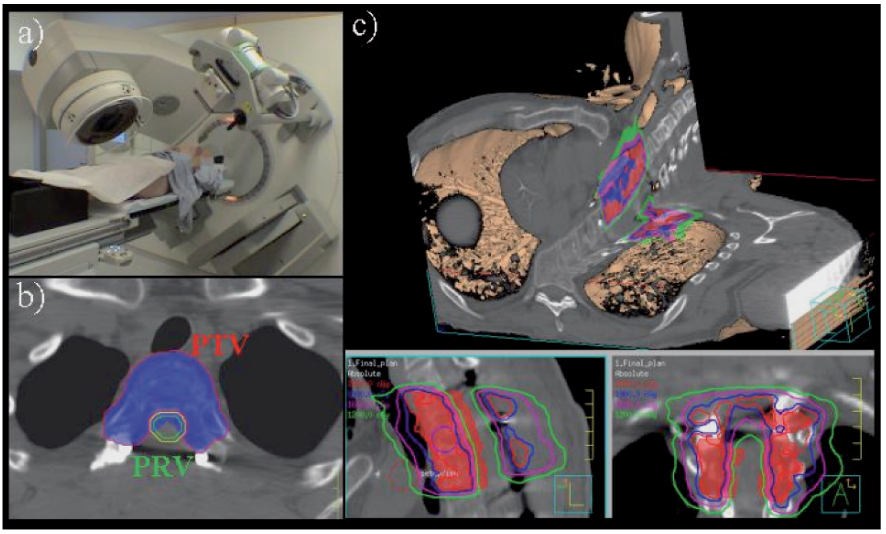

Fig. 17.6. Stereotactic radiation surgery of the spine allows conformality of the target while avoiding the dose-constraining spinal cord. (**a**) The use of image guidance approaches such as cone-beam CT to guide therapy allows use of small PTV margins [see inset (**b**)] and opportunities to spare the cord. (**c**) The use of intensity modulated radiation methods results in highly conformal dose distributions that satisfy the competing objectives of the prescription. While image guidance allows increased conformality, it also provides an accurate record of the treatment to allow for safe retreatment should the need arise

(i) the adaptation dynamic and (ii) the "user as innovator" dynamic as described by W. Lowrance in Ekelman [1988].

17.6.1 Image Guidance, Adaptation, and Innovation by the User

The "adaptation dynamic" is related to the rising availability of information about the patient during the course of intervention. Conventional medical practice is founded on the principles of prognostication [Gospodarowicz and O'Sullivan 2003]. In medical practice, determination of best intervention requires the "freezing" of various prognostic factors to allow timely and appropriate decision making regarding the course of therapy for an individual. Failure to "freeze" the many variables results in endless pursuit of more or "better" information to increase confidence in the predicted outcome, given a specified intervention. Simultaneously, failure to freeze the variables may also result in a loss of opportunity to intervene.

Identification of this fundamental element of medical practice is attributed to Hippocrates wherein he highlighted the importance of honesty in the process of observation and prediction of patient outcome. The development of methods of monitoring or assessing the patient over the course of

therapy continues on this philosophy, but the quantity and quality of the information challenges the practice by contributing knowledge that may require *re-prognostication* of an individual patient's outcome during the course of intervention. The risk, of course, is that these modified predictions may be inaccurate. In the context of image guidance, there is nearly a continuous stream of new information being generated for purposes of improved targeting. Whether this information describes the shrinkage in lung tumor volumes during radiation therapy, the realization that complete resection of the tumor is not possible after initiating surgery, or the documented change in MR imaging signatures (e.g., apparent diffusion coefficient) after intervention, inconsistencies between this information and the observations used in the initial prognosis will drive adaptations to the intervention, and put immense pressure on the physicians' capacity to predict outcome for the individual at the onset of therapy. Furthermore, it will make trials-based assessment of the method difficult due to variations in clinical management. Regardless of whether we have the training and tools to deal with this new information, it has begun to arrive through the deployment of image guidance technologies and can be expected to increase. Furthermore, it can be anticipated that the integration of more advanced imaging tools will produce a greater temporal density of this information and significantly stress the traditional prognosis-treat-assess cycle that is at the foundation of modern healthcare.

The second dynamic of interest is that of the "user as innovator." While this concept is mature and highlighted by Lowrance in 1988, its relevance is elevated by the adaptation dynamic described above. Lowrance's comments are in the summary of an interesting and insightful publication entitled *New Medical Devices: Invention, Development, and Use* [Ekelman 1988] This publication arose from a National Academy of Engineering/ Institute of Medicine symposium chaired by Robert W. Mann of MIT and Walter L. Robb of the General Electric Company.

In his review of the process of medical device development, Samuel Thier presents a strong case for the central role of the user in development of medical devices, as opposed to industry-initiated developments. Through a review of previous studies, he reinforces that the estimates of 80% of all device developments are instigated by the user. A leader in the identification of this process, E. von Hippel has recently reported commercial successes associated with leveraging this dynamic in a corporate strategy in 3M's medical–surgical division.

Lowrance's synopsis of the entire symposium reduces to a few identified needs and opportunities, wherein, he identifies the "most neglected step in the innovation scheme" as that of the "last long feedback loop: the one from the ultimate user community back to the start of the whole process." Given the importance of the role of the user in this process, what can be done to facilitate this dynamic?

17.6.2 Environments and Conditions that Support Innovations in Image-Guided Therapy

In terms of funding, there are a number of initiatives put forward in the past 10 years to foster health care innovation within the imaging and intervention communities. These include targeted funding opportunities as well as institutional initiatives. The U.S. National Institutes of Health (NIH) have initiated a number of calls for applications in the area of image-guided interventions in cancer. This has been primarily supported by the National Cancer Institute (NCI) with support of the recently formed National Institute of Biomedical Imaging and BioEngineering (NIBIB). The development of the Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs recognize the need for the researchers to take their developments to the commercial setting if they are going to have an impact. These are important initiatives that seek to address the need for funding and also provide mechanisms for the maturation of the technologies to product.

Institutional programs that foster the development of the "user" would be consistent with Lowrance's objectives. An approach that has been developed to better integrate the user within the process of innovation is that of the "clinician scientist." There has been over a decade of angst associated with the reduction in the participation of the clinician in scientific research. The past 10 years have seen dramatic increases in the establishment of dedicated clinician scientist support, with an expectation that these individuals contribute to both clinical and research activities. This has been operational in a number of health care systems throughout the world. For example, Singapore's Agency for Science, Technology, and Research works in collaboration with their Ministry of Health to fund 14 clinician scientists for both basic and translational work. In Canada, the Canadian Institute for Health Research (CIHR) has put forth a series of recommendations in a report entitled *The Clinician Scientist: Yesterday, Today, and Tomorrow*. Recommendations such as …develop a national framework (language) for what we mean by clinician-scientist… and …[collect] up-to-date statistics that speak to the composition of the clinician-scientist community… clearly indicate that they seek to maintain a level of clinician involvement in the national biomedical research agenda. It is quite clear from their report that the term "clinician" is not restricted to a physician. They go on to recommend that non-MDs be included in this definition and the development of research activities in this component of the healthcare system also be aggressively pursued. While it is evident that efforts are being made to improve clinician/user involvement in the research agenda, one can still ask "Is medical device development sufficiently supported through these programs?" What is the appropriate training for a clinician scientist if medical device development is to be a successful outcome? Are these clinician scientists providing the "last long feedback loop" for medical

device development or are they preferring to focus on the basic science of the disease – an important contribution, but not targeted at device development. Given the multidisciplinary nature of intervention and the complexity of these interventions, it is difficult to imagine the Lowrance's user is actually an individual. Rather, it has become a team that collaborates for healthcare delivery and that this team needs to be fostered and supported in their pursuit of improved health care delivery. One could extend the concept of the clinician scientist to reflect the reality of current health care practice and seek to develop "clinical science teams." In the context of cancer, the relationship between physician and physical scientist (physicist) has been a long-standing and fruitful collaboration. In the context of radiation oncology, this relationship reaches back to the start of technology development in radiation oncology. For example, the collaboration of Henry Kaplan, M.D., and Edward Ginzton, Ph.D., led to the development of the medical linear accelerator at Stanford University and first treatment in 1957, and the development of the Gamma knife unit by the team of Lars Leksell, M.D., and Borje Larsson, Ph.D., in 1968. The changing nature of medical device technology suggests that collaborative relationships with computing and material sciences should be stimulated and fostered.

There have been a number of initiatives to establish infrastructure to foster clinical science teams in image guidance. Examples of which include the Center for Integration of Medicine and Innovative Technology (CIMIT) in Boston, USA (http://www.cimit.org/), the Centre for Surgical Technologies and Advanced Robotics (CSTAR) in London, Canada (http://www.cstar.ca), and the recently initiated Spatio-temporal Targeting and Amplification of Radiation Response (STTARR) program in Toronto, Canada (http://www.sttarr.ca/). Dedicated laboratories that allow the clinician (surgeon, radiation oncologist, physicist, therapist) to test and mature concepts before returning to the clinical environment are critical for the team to progress. Often the technologies employed in these activities are remarkably similar across treatment modalities. The Guided Therapeutics (GTx) Program is a new initiative at the University Health Network and this program seeks to provide a communication channel between disciplines (surgery, radiation, interventional radiology) and among researchers (clinicians, physicists, engineers, computer scientists) to avoid duplication of skill-sets and solutions. This program has harmonized its funding pursuits to develop a common laboratory environment for preclinical work with corresponding clinical facilities that will accept these novel approaches. While the infrastructure is usually perceived to be related to walls, devices, and the like, the greater challenge is in achieving support for these novel approaches in the demanding context of an active hospital with resource constraints. This particular challenge can only be addressed by engaging the senior management of the institution and articulating the value of innovation for the benefit of the patient and the hospital or health system as a whole.

Ultimately, if the initiative is to be successful, the team must reflect all stakeholders (e.g., administration, nursing, biomedical engineering, facilities) and cannot be restricted to the user, the scientist, or the physician.

17.7 Conclusion

The challenge of executing the localized cancer intervention continues to drive innovation in the field of oncology. The development of adaptable imaging systems that can integrate within the interventional setting is allowing these interventions to be applied under guidance for the benefit of both increased probability of cure, as well as the potential for reduced toxicity. The interventions of radiation therapy and surgery are by far the dominant form of local intervention in oncology and these two fields are rapidly adopting image guidance approaches. The "new information" provided in the context of image guidance will not only lead to increased accuracy in intervention, but also create a dynamic course for therapy in which interventions are modified or adapted to the individual patients response. These activities will put immense pressure on the current treatment paradigm and drive the development of devices, like new software tools, and the desire for more robust biological models to guide this adaptation. Despite these concerns, there is genuine potential for the image-guided approaches to become the standard of care. This transition will challenge the traditional educational and operational paradigms of oncology intervention and additional effort must be invested in the development of programs to facilitate the maturation and adoption of image-guided approaches.

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