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Technical Aspects of Positron Emission Tomography/Computed Tomography Fusion Planning

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Emerging technologies in radiation therapy computers and delivery systems allow surgically precise conformal radiation treatment that was not possible with previous generations of equipment. The newest treatment systems can compensate for tumor target motion as well as shape dose distributions to conform precisely to delineated target volumes. These sophisticated technologies now drive the development of imaging modalities able to generate equally high-resolution and lesion-specific roadmaps that are the foundation of these highly accurate radiation plans. Positron emission tomography/computed tomography (PET/CT) is currently becoming a routine imaging tool for radiation oncology because of its combined benefits of positron imaging and high-resolution anatomic display. The improved staging and lesion delineation provided by PET, combined with the 3D anatomic display provided by CT, now allows better treatment stratification and more precise targeting. Additionally, respiratory-gated 4D CT and 4D PET/CT have been used in the simulation process for respiratory-gated radiation therapy. Successful integration of PET/CT into the radiation therapy planning process requires an understanding of how therapy plans are derived and the process by which the patient receives therapy, because these dictate the method of image acquisition. The radiation oncologists, too, must understand the technology of positron imaging to adapt these functional images based on intensities rather than pixels to their targeting process. Modifications to the PET/CT scanner and room are necessary to image the patient in the reproducible position required for treatment planning. Although the impact of these efforts on patient outcome has yet to be determined, the benefit of better treatment choice, due to improved staging, and more precise targeting with less normal tissue exposure resulting in improved quality of life will likely promote PET/CT to the gold-standard for targeted therapies.
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Multimodality imaging in radiation therapy planning combines two or more imaging technologies to provide complementary data, enabling tumor targeting in a manner not possible with a single modality. Anatomic imaging with computed tomography (CT) or magnetic resonance imaging can be fused with the functional information provided by positron imaging or magnetic resonance spectroscopy to optimize tumor delineation. Consequently, anatomic-biologic tumor targeting achieved with positron emission tomography (PET)/CT is fast becoming an accepted and routine clinical tool in radiation therapy planning. With continuing innovations in PET/CT technology and the increasing availability of these scanners, integration into the radiotherapy work-flow is now easily achievable. It is the unique combination of improved staging accuracy and tumor delineation that is provided by PET/CT, however, that is making this modality a requisite for state of the art therapy planning. Current radiotherapy planning systems have the capability of integrating and manipulating extraordinary amounts of 3-dimensional data to produce surgically precise dose targeting and delivery to the tumor bed. Moreover, with the introduction of image-guided radiation therapy (IGRT), a technology that permits inter- and intrafractional beam alterations based on tumor motion, confidence and accuracy in targeting is crucial.

Although sufficient outcome statistics have yet to be accumulated, the value of incorporating PET/CT in the radiotherapy planning process is clearly established in lung and head and neck malignancies.[1-7] Published data also suggest improvements in the imaging of esophageal, rectal, and cervical cancers.[8-11] Benefits derived from PET/CT simulation arise

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from more precise delineation of the primary tumor target and include target volume changes resulting from more accurate detection of local nodal disease. An additional advantage of optimized target definition is decreased radiation dose to the adjacent normal tissues. It is the superimposition of the tumor metabolic activity on its exact anatomic location depicted with CT that is the key to achieving the full impact of the current high-precision radiation therapy delivery systems. With focused delivery methods, such as intensity-modulated radiation therapy and IGRT, it is possible to increase the therapeutic ratio, ie, maximize the dose to tumor without increasing toxicity to nontumor-bearing tissue.

Interobserver variability in tumor contouring among radiation oncologists is known to be a factor that may adversely affect a radiation plan.[12] A distinct decrease in inter- and intraobserver observer variation in tumor contouring is seen with the introduction of functional PET imaging in radiation simulation.[13,14] The conventional approach of CT simulation for tumor targeting may introduce geometric uncertainties into a radiation plan because of difficulties in determining tumor margins, (eg, a nonsmall-cell lung cancer within a segment of atelectatic lung), and because of the limitations of cross-sectional CT in the identification of tumor-bearing local lymph nodes. PET images registered, or fused, with CT images enhance the contouring process by providing radiation oncologists with a "metabolic target." Fox and coworkers showed more consistent contouring among radiation oncologists with computer-fused images rather than with simple visual comparison of side-by-side images. When comparing the tumor volumes independently contoured by 3 radiation oncologists, the authors found a greater concordance among the physician's target delineations of nonsmall-cell lung cancer when contouring was performed on registered images versus when contouring was performed on CT with the PET images displayed on a separate workstation.[15]

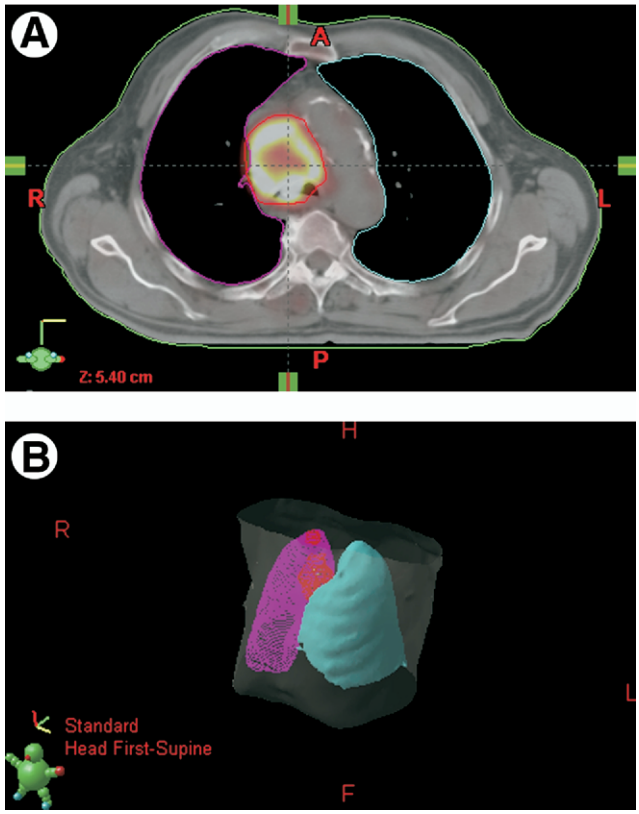

Figure 1 (A) Axial fused image from a PET/CT performed for radiation therapy planning, displayed on the RT workstation for a patient with nonsmall cell lung cancer. The red contour defines the margins of the mediastinal malignancy, the GTV, or BTV. The lungs are contoured to identify normal radiosensitive structures. (B) A 3D display of the same patient displays the relationship of the radiosensitive lungs to the mediastinal tumor target emphasizing the importance of the relationship of the metabolic activity to the 3D anatomy.

Basics of Tumor Targeting and Planning

To understand the full impact of combined anatomic-biologic imaging in radiation therapy planning, it is necessary to have a basic understanding of how radiation targets are defined and how therapy plans are developed.[16-18] The visual extent of the primary tumor as depicted on CT is termed the gross tumor target, or GTV. With the introduction of functional imaging the concept of biologic target volume or BTV has been introduced (Fig. 1).[19-21] To compensate for suspected microscopic spread of tumor, a 1- to 2-cm expansion, termed the clinical target volume (CTV) is added to the GTV. The size of this added volume is based on pathologic and physiologic data of microscopic tumor infiltration and tumor location. The final volume, the planning target volume, PTV, is a further expansion of the CTV compensate for voluntary and involuntary patient motion, uncertainties regarding microscopic disease and day to day inaccuracies that relate to patient positioning (Fig. 2). The PTV excludes defined regions that identify the normal surrounding tissues, ie, the organs at risk. These are tissues that are radiation sensitive and exposure in the treatment field will result in posttreatment morbidity. Therefore, these organs at risk, the spinal cord, bladder, rectum, lung, heart, kidneys, and salivary glands, are delineated on the treatment planning computer by the radiation oncologist and dosimetrist to be excluded from the treatment field. The final radiation plan is then computer generated on an inverse determination of the maximal allowable dose to the normal tissues. In this way, the radiation oncologist prescribes the maximal allowable dose to the normal tissues and this dose then determines the maximum radiation dose that can be delivered to the tumor target (Fig. 3).

Radiation Therapy Simulation

Imaging tools for radiation planning have evolved from simple visual inspection and manual palpation of the late 19th century to current complex three dimensional renderings that create a virtual patient model from which multiple beam, volumetric plans are derived. Regardless of the complexity of the imaging used, there are certain key components of the radiation therapy simulation process that are critical in en-

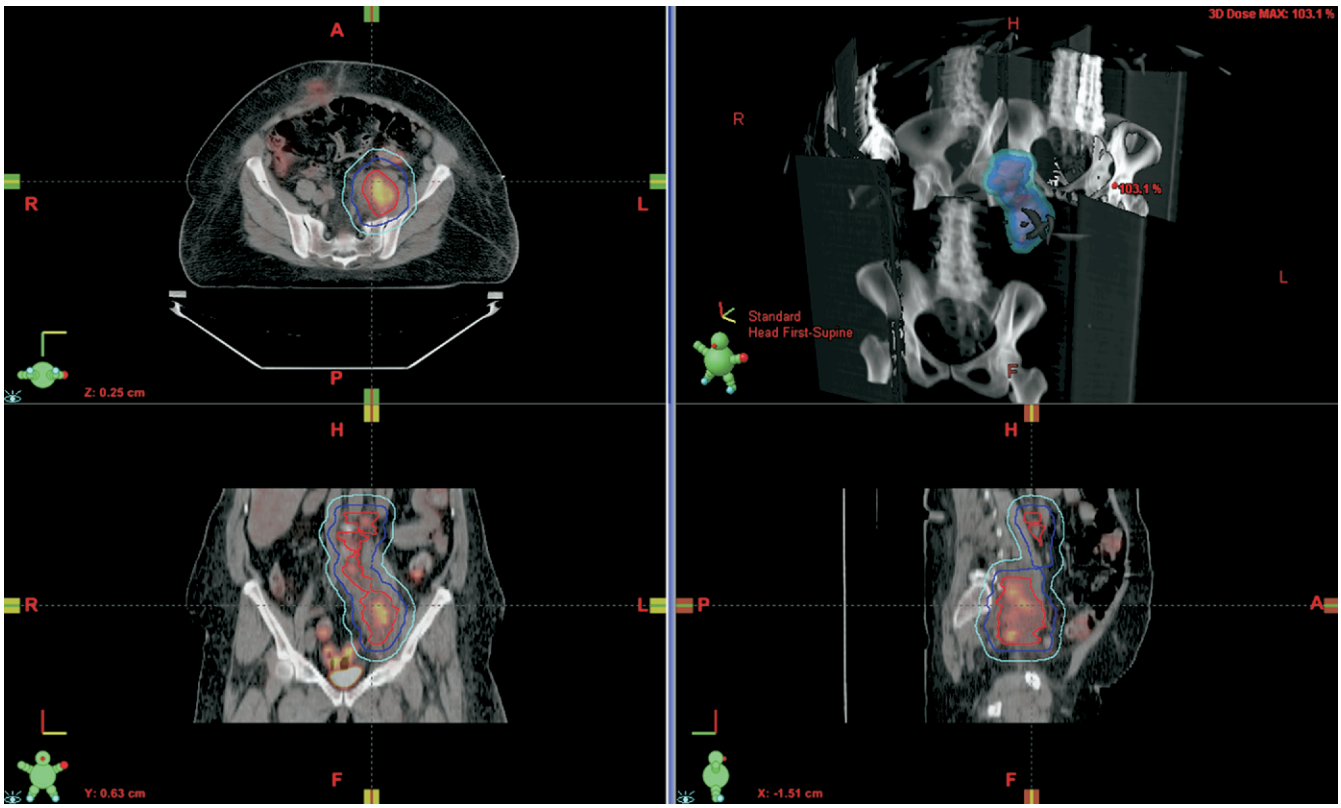

Figure 2 Multidimensional display from the RT workstation demonstrates the 3D contours defining pelvic and retroperitoneal metastases in a 63-year-old patient with recurrent endometrial cancer. The red contour defines the GTV, the blue contour defines the 3D expanded CTV, and the turquoise contour delineates the further expanded PTV.

suring that the target will receive the prescribed dose. Of paramount importance is the ability to image the patient in the exact position in which therapy will be delivered. The simulation process generally involves the fluoroscopic or CT identification of the tumor location and the placement of an anterior and lateral setup field. The point of intersection of these fields is to the center of rotation of the linear accelerator, the isocenter. Indelible reference points are placed on the patient's skin that will be aligned with wall-mounted lasers to ensure the patient position is unchanged with each daily treatment. Immobilization of the patient is achieved by the creation of a variety of patient-specific devices, such as thermoplastic molds, alpha cradles and vac-loc bags, within which the patient will be placed for each therapy session. All preparation and therapy is performed with the patient on a flat table and the immobilization device locked in the same position on the table. For each daily treatment session, patient position is confirmed with portal radiographs or on-board imaging such as cone-beam CT or KV imaging, generated directly from the linear accelerator.

PET/CT Simulation

A PET/CT performed for radiation therapy planning is a limited examination of 1 to 2 table positions, ensuring adequate coverage of the area to be targeted. This may be acquired as a separate examination, or, performed as part of a whole-body scan, if the patient can tolerate immobilization for the whole body acquisition time. After patients undergo an overnight fast, they are injected with a standard dose of 15 to 20 mCi (555 to 740 MBq) ^{18}F-fluorodeoxyglucose (FDG) before or after isocenter determination and fabrication of the appropriate immobilization device. If department efficiency and personnel requirements dictate that the first part of the simulation is to follow tracer administration, the time interval of the uptake period will be dictated by the length of time required for the first part of the simulation. A minimum period of 30 minutes quiet uptake time with the patient placed on a stretcher or reclining chair, however, is required to allow sufficient tracer blood-pool clearance to prevent excessive muscle uptake resulting from patient motion.[22]

To optimize the utilization of a PET/CT scanner for radiation planning, several technical requirements need to be satisfied. They introduce into the PET/CT scanner environment key components of the radiation therapy simulation process. Positioning lasers are installed on the ceiling and both opposing walls of the PET/CT scanning room. These lasers are sited according to the PET/CT gantry isocenter. The PET/CT scanner is equipped with a flat table that can be locked in place in the scanning bed. The table, marked with numerical position indicators, can accommodate the fixation of the various immobilization devices. For the PET/CT simulation session, the patient is positioned on the flat table as he or she would be positioned for therapy. This positioning is achieved by alignment of the isocenter markers with the laser cross-beams and

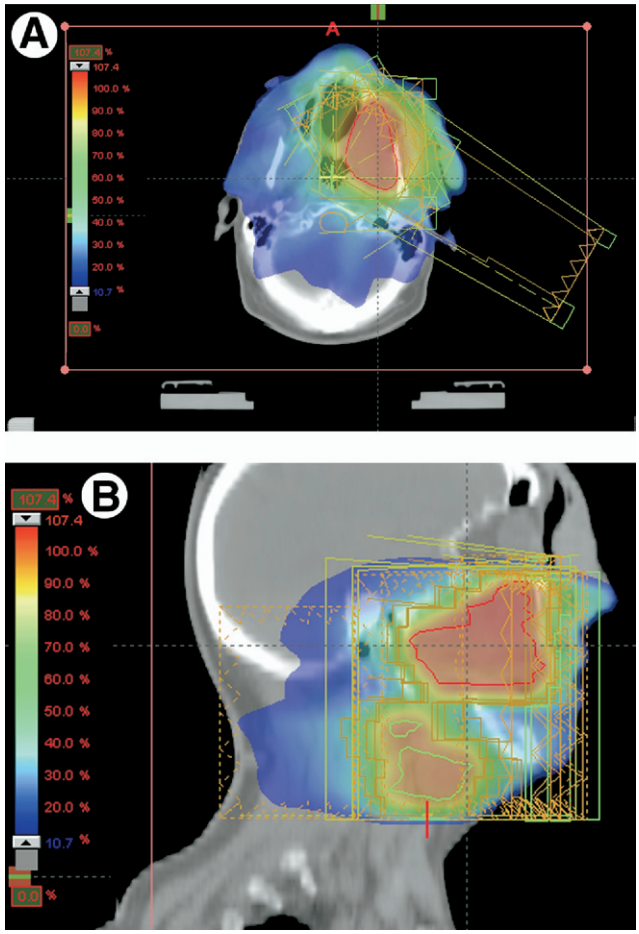

Figure 3 IMRT plan defined on fused PET/CT axial (A) and sagittal (B) displays for a patient with head and neck squamous cell cancer, color coded to indicate radiation dose. The therapeutic dose, red, is localized to the PET-positive primary tumor. The regions of the right parotid and spinal cord are exposed to levels less than 20% of the prescribed tumor dose, well within tissue tolerances.

correlated with the table position, thus duplicating the treatment position. The positioning function may be performed by both the radiation therapy technologists and by trained PET/CT technologists. Because these technologists are working at close range with patients who have been injected with a positron emitter, close monitoring of exposure and strict adherence to ALARA principles are warranted.

The actual acquisition parameters for the simulation PET/CT will be dependent on the scanner used. Although the optimum CT slice thickness for radiation therapy simulation is 1.25 to 2.5 mm, CT slice thickness will default to 4.25 mm to match the PET slice thickness to facilitate fusion of the PET and CT images.

Respiratory-Gated Radiation Therapy: 4D PET/CT Simulation

Tumor targets in the thorax and upper abdomen move with a patient's respiration, in some cases, as much as 2 to 3 cm in the cranio-caudal direction.[23,24] The superior and inferior margins of treatment fields, determined by static conventional imaging that displays tumor location at only one time point, are estimated to encompass assumed target motion and typically translate to at least a 2-cm expansion of the CTV. Because of the uncertainties of tumor position during the respiratory cycle, radiation oncologists have had, in the past, no alternative but to treat larger volumes of normal tissue resulting in higher likelihood of damage to the structures in close proximity to the tumor. Much more critical is the potential undertreatment of the edges of the tumor, because it may move beyond the prescribed boundaries of the radiation field.

Respiratory-gated RT (RGRT), one of a number of emerging technologies referred to as IGRT, is a treatment technique that synchronizes the delivery of the therapeutic radiation dose to a selected phase of the patient's respiratory cycle, either end-inspiration or end-expiration. With the target volume minimized, normal tissue exposure is reduced and a greater dose to the tumor target may be possible.[25-28] This technique requires simulation imaging that can provide the spatial and temporal information necessary to develop therapy plans that target a lesion at a predetermined phase of the respiratory cycle. Breath-hold CT, respiratory-gated CT (4D CT), or respiratory-gated PET/CT (4D PET/CT) can be used for this purpose.[29] There is not one optimal method yet identified as most appropriate for RGRT. Some patients are physically unable undergo a respiratory-gated imaging session, and simple breath hold methods can prove effective. Lorchel and coworkers, evaluated end-inspiration, end-expiration, deep inspiration, and free-breathing spiral CT scans for simulation imaging of 8 patients with esophageal squamous cell cancer. The authors compared the dose volume histograms for the PTV and the organs at risk for each conformal radiation plan. The found that the radiation dose to the heart and lungs was less with RGRT plans developed with deep inspiration breath-hold and end-inspiration breath hold in comparison to plans derived with free-breathing CT.[30]

The 4D imaging is a sequential set of 3D imaging studies broken into groupings by some external signal, called the surrogate signal. This signal may be an external marker block placed on the patient's chest or abdomen, a spirometer tidal volume measurement, or other methods that can correlate to the phase of respiration and indirectly, the tumor's location. There are 2 different types of gated imaging that may be performed for these studies. Prospectively gated imaging allows the imaging device to accumulate data only during the period of interest by triggering the acquisition to occur when the surrogate signal is at the proper position or time. Retrospective gating resorts multiple scans obtained over the entire respiratory cycle into bins based on the surrogate signal's position or time. Another subdivision of these types of imaging is the choice of whether one wants to use the position of the surrogate signal (called amplitude gating) or the periodic relationship between inhalation and exhalation (assuming that the patient is being prompted to reproducibly breathe in and out). This type of gating is called phase gating.

The imaging protocol for 4D imaging consists of many steps necessary to assure proper patient selection and reproducibility and will be dictated by the technology and method of the delivery system. In our institution, 4D PET/CT images

are acquired using the same technology that produces the respiratory signal for radiation delivery. The first step in the process is done during the initial simulation of the patient. At this time, the patient is placed in the treatment position, a custom immobilization device is constructed, and a passive marker block is placed on the chest or abdomen. This marker block will serve as the surrogate signal for both the imaging and treatment sessions. A patient gating assessment is then performed to determine whether the patient can perform the necessary inhalations and exhalations for the gated imaging session and treatment. The patient is coached during multiple respiratory cycles, during which an audio prompt instructs the patient to breathe in and breathe out at a set time interval. If fluoroscopy is available, it can also be helpful in approximately assessing the extent of tumor motion. The imaging and treatment sessions can last 6 to 8 minutes and can be difficult for some patients to comply with the repetitive breathing commands. For patients that cannot perform many breaths in succession, breath hold methods may be required.

For the 4D imaging session, the same injection and uptake protocol previously described for the PET/CT simulation is used. The patient is placed in the immobilization device created previously and put into the same audio prompting that was determined during the breathing assessment. The 4D PET is performed using 1 bed position with the imaging being triggered by the external gating system (prospective gating) for a total time of 6 to 8 minutes of imaging time. After processing on the PET reconstruction console, a set of 5 to 10 PET studies is created. The next step is the 4D CT imaging session, which consists of the same patient position and breathing prompts as the 4D PET. A cine CT acquisition is performed (imaging time is 4-5 minutes) with the gating system recording the marker block position and time for later use (retrospective gating). This imaging session results in a CT scan with 1,500 to 2,500 images that were taken sequentially but the position or time relative to the patient's breathing cycle is not known. This cine CT data set is then transferred to the CT simulation computer, which has special software loaded that "marries" the cine CT data set to the surrogate signal of the patient and re-sorts the cine CT into a series of sequential CT sets based on the patient's surrogate signal.

Data Transfer

The acquired PET and CT images acquired during the simulation session are exported separately from the PET/CT workstation to the radiation therapy workstation or virtual simulation station. The procedure for data transfer of 4D PET/CT will be specific to the vendor. DICOM compatibility between the PET/CT scanner and the radiation therapy workstation is an important requirement to ensure seamless transfer of data from the PET/CT to the workstation. Logistical issues arise in instances in which imaging is being performed in a location remote to the radiation oncology department and in these instances transfer of separate digital PET and CT images can be accomplished via network connections or hard copy disc. Commercially available software provides the capability to fuse PET/CT data that was performed at an earlier date to a newly acquired simulation CT. In addition, some planning or virtual simulation systems have the ability to allow a previously acquired PET/CT to be reformatted in the same geometry as a new simulation CT to allow fusion of the old and new data sets. Such software can be invaluable in instances where reimbursement issues prohibit a PET/CT simulation scan due to a prior recent PET or PET/CT study having been performed for diagnosis or staging.

Contouring

Despite the wide acceptance of PET/CT by the radiation therapy community, the actual integration of PET images into the tumor target contouring process has been problematic. The lower resolution and poorly defined lesion edges inherent in positron images introduce uncertainty, compounded not only by variation and heterogeneity in lesion metabolic activity but also by the effects of display intensity that can artificially alter lesion size and conspicuity (Fig. 4). Visual interpretation of PET images by an experienced nuclear medicine physician who then sets display intensity for contouring is one approach. Another approach is to use the PET data to direct contouring of CT image set. This is typically achieved on a PET/CT workstation and exported to the radiotherapy planning computer. Recently, has it become possible to contour the fused data sets, ie, color-displayed PET overlaid onto CT image, and this practice is the one most often used at our institution.

In facilities where contouring is performed on the radiation therapy treatment planning computer, this task is further complicated by the inability of the planning software to display SUV data, because voxels of PET activity are converted to intensity levels. In an attempt to address these problems, several authors have devised methods to automate and standardize the PET display by various methods of thresholding lesion SUV_{max}. The effect of size on threshold is reported by Davis and coworkers, in a phantom study of a model-based method developed to determine a relative threshold level (Th(rel)) that assumes a uniform signal from the lesion and the surrounding tissues and then generates a volume based on this threshold.[31] The (Th(rel)) of 41 ± 2.5% of background subtracted signal best approximated the true source diameter and was constant for diameters greater than or 12.5 mm. For source diameters less than 12.5 mm, the 41% (Th(rel)) overestimated the diameter based on a factor that was diameter dependent.

PET-based tumor volumes are strongly affected by the choice of threshold and will result in significant changes in target radiation dose. Ford and coworkers, applied an automated contouring function based on progressively greater threshold levels to the coregistered PET/CT images of eight head and neck cancer patients and to a phantom containing 6 FDG-filled spheres.[32] Intensity-modulated radiation therapy and boost plans were developed for all GTVs. The authors found a significant effect on GTV volume as a result of choice

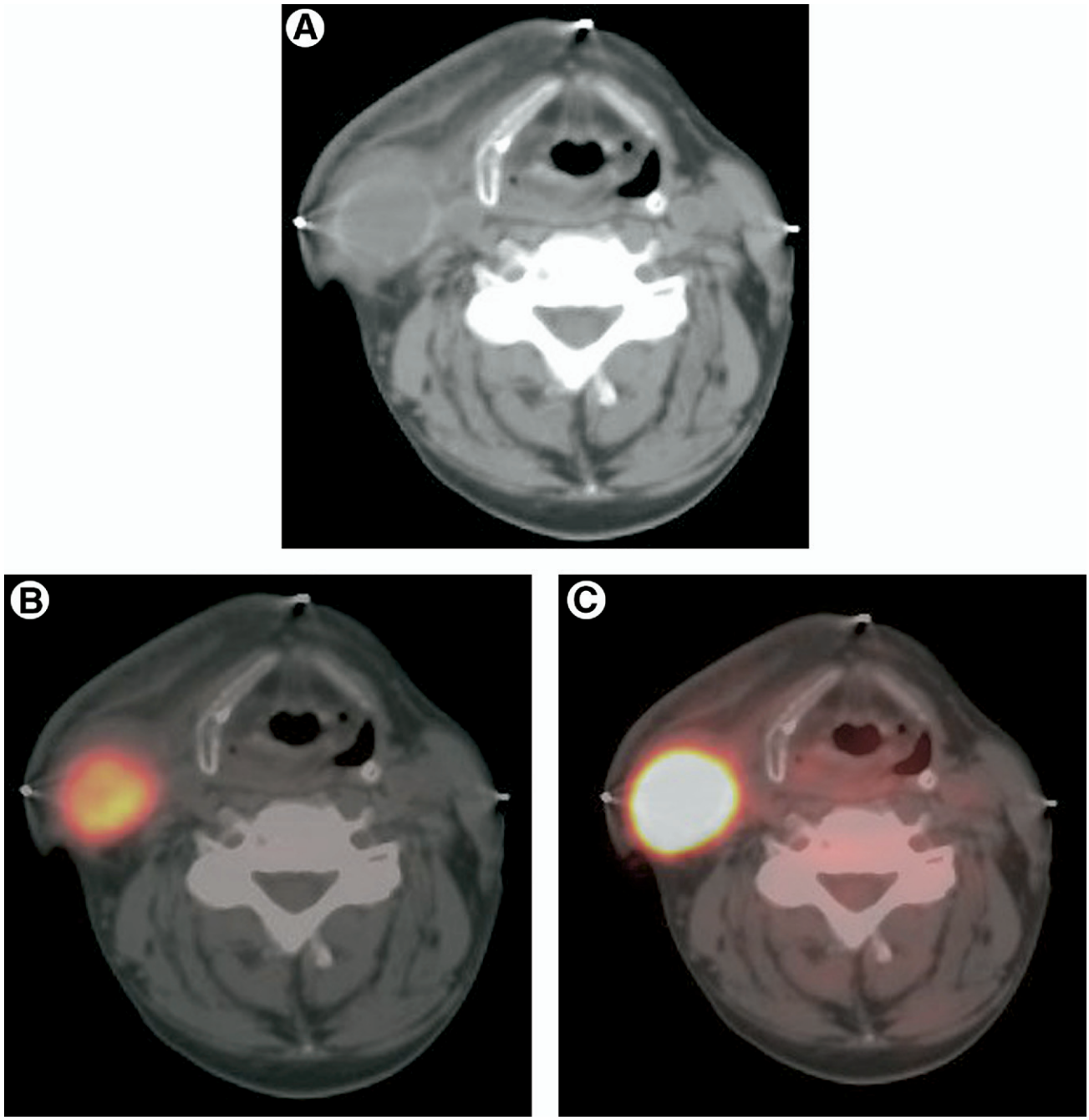

Figure 4 Axial images from a PET/CT performed on a patient with squamous cell cancer of the right pyriform sinus, metastatic to right cervical nodes. The PET/CT is obtained for restaging and RT planning after completion of a course of platinum-based chemotherapy. (A) the axial CT image displays residual tumor in the right cervical region, deep to the sternocleidomastoid muscle. (B) the fused PET/CT with PET intensity set at a low level demonstrates the metabolic activity to approximate the CT boundaries of the mass. (C), the same image set with high PET intensity, expands the metabolic activity beyond the actual anatomic margins.

of threshold level. This translated into significant dosimetric effects resulting from the volume alterations.

A software program that generates contours based on lesion and background intensities has been developed by Nestle and coworkers.[33] The authors report a comparison of 4 methods of determining GTV for nonsmall cell lung cancer and found that GTV_{40} had the poorest correlation with GTV derived from CT in well-defined lesion. The authors suggest that as substantially different volumes will result from various threshold contouring programs, more complex, system-specific algorithms should be investigated. To date, published data are limited in that comparisons of derived PET GTVs are with either CT or FDG-filled phantom spheres. There is only one published article in which authors evaluated the relative accuracy of PET-based volumes in comparison with other imaging modalities using surgical specimens

as the gold standard. Daisne and coworkers, using proprietary software, retrospectively delineated FDG-PET–based GTVs, CT-based GTVs, and magnetic resonance imaging-based GTVs for pharyngolaryngeal squamous cell tumors.[34] PET contours were derived automatically using a segmentation algorithm, based on the relationship between source to background. The authors report that the GTV derived from the FDG-PET images most accurately matched the volumes of the surgical specimens.

The issue of edge inaccuracies in PET-based contouring of GTVs may be a moot point at this time. With routine therapy plans, CTV and PTV contours are added to the GTV that more than cancel any PET edge inaccuracy. However, with the development of increasingly complex plans that correct for motion, ultimately including stereotactic body radiosurgery therapy, as well as multidimensional plans targeting intratumoral variations in a molecular environment, such millimeter accuracy is critical. The development of proven, commercially available automated edge-detection software that can compensate for tumor size and heterogeneity will become invaluable to enhance both accuracy and efficiency.

Conclusion

Integrating PET/CT fusion imaging into an already-established radiation oncology program can be challenging because of technical, administrative, financial, geographic, and personnel issues. The interdisciplinary nature of this approach requires cooperation at multiple levels between imaging and radiation oncology departments. With the promise of new radiopharmaceuticals that can better define cellular activity and hypoxia, the fruits of this effort will contribute toward the ultimate goal of individualized cancer therapies based on patient and tumor molecular characteristics.

References

1. Nestle U, Walter K, Schmidt S, et al: 18F-deoxyglucose positron emission tomography (FDG-PET) for planning in radiotherapy in lung cancer: High impact in patients with atelectasis. Int J Radiat Biol Phys 44:593-597, 1999
2. Vanuytsel LJ, Vansteenkiste JF, Stroobants SG, et al: The impact of ^{18}F-fluoro-2 deoxy-D-glucose positron emission tomography (FDG-PET) lymph staging on the radiation treatment volumes in patients with non-small cell lung cancer. Radiother Oncol 55:317-324, 2000
3. Erdi Y, Rosenzweig K, Erdi AK, et al: Radiotherapy treatment planning for patients with non-small cell lung cancer using positron emission tomography (PET). Radiother Oncol 62:51-60, 2002
4. Bradley J, Thorstad WL, Mutic A, et al: Impact of FDG-PET on radiation therapy volume delineation in non-small cell lung cancer. Int J Radiat Biol Phys 59:78-86, 2004
5. van Der Wel A, Nijsten S, Hochstenbag M, et al: Increased therapeutic ratio by 18FDG-PET CT planning in patients with clinical CT stage N2–N3M0 non-small-cell lung cancer: A modeling study. Int J Radiat Oncol Biol Phys 61:649-655, 2005
6. Schwartz DL, Ford EC, Rajendran J, et al: FDG-PET/CT-guided intensity modulated head and neck radiotherapy: A pilot investigation. Head Neck 27:478-487, 2005
7. Wang D, Schultz CJ, Jusinic PA, et al: Initial experience of FDG-PET/CT guided IMRT of head and neck cancer. Int J Radiat Oncol Biol Phys 65:143-151, 2006
8. Lin LL, Mutic S, Low DA, et al: Adaptive brachytherapy treatment planning for cervical cancer using FDG-PET. Int J Radiat Oncol Biol Phys 67:91-96, 2007
9. Leong T, Everitt C, Yuen K, et al: A prospective study to evaluate the impact of FDG-PET on CT-based radiotherapy treatment planning for oesophageal cancer. Radiother Oncol 78:254-261, 2006
10. Ciernik IF, Huser M, Burger C, et al: Automated functional image-guided radiation treatment planning for rectal cancer. Int J Radiat Oncol Biol Phys 62:893-900, 2005
11. Moureau-Zabotto L, Touboul E, Lerouge D, et al: Impact of CT and 18F-deoxyglucose positron emission tomography image fusion for conformal radiotherapy in esophageal carcinoma. Int J Radiat Oncol Biol Phys 63:340-345, 2005
12. Weiss E, Hess CF: The impact of gross tumor volume (GTV) and clinical target volume (CTV) definition on the total accuracy in radiotherapy theoretical aspects and practical experiences. Strahlenther Onkol 179:21-30, 2003
13. Caldwell CB, Mah K, Ung YC, et al: Observer variation in contouring gross tumor volume in patients with poorly defined non-small-cell lung tumors on CT: The impact of 18FDG-hybrid PET fusion. Int J Radiat Oncol Biol Phys 51:923-931, 2001
14. Steenbakkers RJ, Duppen JC, Fitton I, et al: Reduction of observer variation using matched CT-PET for lung cancer delineation: A three-dimensional analysis. Int J Radiat Oncol Biol Phys 64:435-448, 2006
15. Fox JL, Rengan R, O'Meara W, et al: Does registration of PET and planning CT images decrease interobserver and intraobserver variation in delineating tumor volumes for non-small-cell lung cancer? Int J Radiat Oncol Biol Phys 62:70-75, 2005
16. Van Kampen M, Levegrun S, Wannenmacher M: Target definition in radiation therapy. Br J Radiol 70:25-31, 1997 (suppl)
17. Vanden Berge DL, Ridder MD, Storme GA: Imaging in radiotherapy. Eur J Radiol 36:41-48, 2000
18. van Baardwijk A, Baumert BG, Bosmans G, et al: The current status of FDG-PET in tumor volume definition in radiotherapy treatment planning. Cancer Treat Rev 32:245-260, 2006
19. Ling CC, Humm J, Larson S, et al: Towards multidimensional radiotherapy (MD-CRT): Biological imaging and biological conformality. Int J Radiat Biol Oncol Phys 47:551-560, 2000
20. Bucci KM, Bevna A, Roach M: Advances in radiation therapy: Conventional to 3D, to IMRT, to 4D, and beyond. CA Cancer J Clin 55:117-134, 2005
21. Zanzonico P: PET-based biological imaging for radiation therapy treatment planning. Crit Rev Eukaryot Gen Expr 16:61-101, 2006
22. Bertoldo A, Peltoniemi P, Oikonen V, et al: Kinetic modeling of [^{18}F]FDG in skeletal muscle by PET: A four-compartment five-rate-constant model. Am J Physiol Endocrinol Metab 281:E524-E536, 2001
23. Wolthaus JW, van Herk M, Muller SH, et al: Fusion of respiration-correlated PET and CT scans: Correlated lung tumour motion in anatomical and functional scans. Phys Med Biol 50:1569-1583, 2005
24. Caggiano A, Vialotti C, Brunetti J: 4D PET/CT: Early observations and impact in radiation therapy planning for lung cancer. Int J Radiat Oncol Biol Phys 60:290 (abstr)
25. Wurm RE, Gum F, Erbel S, et al: Image guided respiratory gated hypofractionated stereotactic body radiation therapy (H-SBRT) for liver and lung tumors: Initial experience. Acta Oncol 45:881-889, 2006
26. Giraud P, Yorke E, Ford EC, et al: Reduction of organ motion in lung tumors with respiratory gating. Lung Cancer 51:41-51, 2006
27. Underberg RW, van Sornsen de Koste JR, Lagerwaard FJ, et al: A dosimetric analysis of respiration-gated radiotherapy in patients with stage III lung cancer. Radiat Oncol 1:8, 2006

28. Butler LE, Forster KM, Stevens CW, et al: Dosimetric benefits of respiratory gating: A preliminary study. J Appl Clim Med Phys 5:16-24, 2004
29. Keall PJ, Mageras GS, Balter JM, et al: The management of respiratory motion in radiation oncology report of AAPM Task Group 6. Med Phys 33:3974-3900, 2006
30. Lorchel F, Dumas JL, Noal A, et al: Dosimetric consequences of breath-hold respiration in conformal radiotherapy of esophageal cancer. Phys Med 22:119-126, 2006
31. Davis JB, Reiner B, Huser M, et al: Assessment of 18F PET signals for automated target volume definition in radiotherapy treatment planning. Radiother Oncol 80:43-50, 2006
32. Ford EC, Kinahan PE, Hanlon L, et al: Tumor delineation using PET in head and neck cancers: Threshold contouring and lesion volumes. Med Phys 33:4280-4288, 2006
33. Nestle U, Kremp S, Schaefer-Schuler A, et al: Comparison of different methods for delineation of 18F-FDG PET-positive tissue for target volume definition in radiotherapy of patients with non-Small cell lung cancer. J Nucl Med 46:1342-1348, 2005
34. Daisne JF, Duprez T, Weynand B, et al: Tumor volume in pharyngolaryngeal squamous cell carcinoma: a comparison at CT, MR imaging and FDG PET and validation with surgical specimen. Radiology 233:93-100, 2004