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The Role of Positron Emission Tomography in Radiation Treatment Planning

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We estimate that 30% to 40% of radiation treatment plans for cancer patients are changed when positron emission tomography (PET) scan findings are factored into the plan. The most frequent changes are upstaging of disease and the finding of new distant metastases. When a tumor demonstrates high tracer uptake, the PET scan has high accuracy in staging and in determining recurrent disease. However, the absence of tracer uptake cannot exclude residual dormant disease. Following radiation therapy, a PET scan should be delayed at least 6 weeks and preferably 3 to 4 months so that inflammation within the radiation field can dissipate. PET has resulted in changes in the gross tumor volume; however, the process remains subjective.

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When a baseline positron emission tomography (PET) scan shows that a tumor has high tracer-avidity, then PET has a high accuracy to stage, to target, and to determine recurrent carcinomas. With new combined PET-computed tomography (CT) scanners, the fused images provide the superior tumor targeting of PET and the precise mapping of CT to define tumor edges. Better imaging means better triage of patients. For patients with localized disease and no evidence of macroscopic disease elsewhere, an aggressive approach may be considered with the intent to cure. In patients with advanced disease, a conservative plan emphasizing palliation of pain and preservation of function is usually adopted. PET scanning tends to upstage most patients, and new sites of disease often are found that require prophylactic radiation to prevent disability or pain. In our experience, approximately 30% to 40% of treatment plans for cancer patients are changed when PET scan findings are factored into radiation therapy planning (RTP). The evaluation of post-therapy patients has been problematic with anatomic imaging modalities alone because typically there is distortion with a loss of symmetry in previously irradiated or surgically altered tissue. With PET, intense tracer uptake strongly suggests recurrent active disease, although absent uptake cannot exclude residual dormant disease. One should wait at least 6 weeks and preferably 3 to 4 months before obtaining a PET scan after radiation therapy so that inflammation within the radiation field can dissipate. PET has resulted in changes in the gross tumor volume; however, the process of determining a gross tumor volume remains subjective.

PET has not replaced the standard imaging modalities, ie, CT, ultrasound, and magnetic resonance imaging (MRI), that are most frequently used by radiation oncologists to target tumors. It has,

however, supplemented these modalities in the detection of tumors and has added a new facet of information that has changed targeting. Most current oncologic PET uses 18-fluorodeoxyglucose (FDG) as the tracer, and in this article PET will imply FDG-PET unless stated otherwise.

A tenant of radiation oncology is that no tumor is able to survive a concentrated dose of radiation. The problem is delivering the dose necessary at the right time while limiting radiation to surrounding normal tissue. How much dose and when depends on the biology of the tumor, and this is where the metabolic information provided by PET is intriguing. How should PET influence the targeting of tumors? Answers will depend on technology to deliver radiation precisely and on outcome studies. Radiation oncology continues to move toward three- and four-dimensional treatment plans that are heavily dependent on volume imaging. Intense narrow multiangle beam delivery and computer optimization plans that track targets and minimize side effects are at the forefront of radiation oncology. Indeed, most all of the newer radiation treatment plans use anatomic three-dimensional imaging—usually CT—to design the delivery of radiation. The ultimate goal of anatomic imaging is to have a scanner that can noninvasively depict a microscopic image of cells and tissue similar to that seen on a pathology slide. However, functional imaging such as PET aspires to characterize “in vivo” physiology. Physiologic properties that could differentiate between susceptibility and resistance to a therapy within a tumor would be critical. The Holy Grail of oncologic imaging would be a device that is able to see both the anatomic and physiologic details of tissue. We are getting closer with the introduction of combined PET-CT scanners. With precision, functional images of PET can be superimposed on the corresponding anatomic images and essentially the PET tracer can be considered a metabolic contrast agent. PET-CT provides high accuracy in detecting a wide variety of carcinomas in patients that are frequently referred for radiation. The advantages it offers over CT and MRI alone in detecting carcinomas of the head

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and neck, lung, esophagus, colon, rectum, cervix, and lymphatics have become obvious to radiation oncologists and have resulted in better triage of their patients.

Scanning for Radiotherapy: The "Simulation" Scan and Gross Tumor Volumes

Most patients referred for PET have already had a variety of conventional imaging and have been diagnosed with carcinoma. Likewise, most patients referred for radiation have biopsy proven disease. Therefore, setting up an initial PET or PET-CT scan for RTP is logical. Such scans are called simulation scans because they emulate the treatment position. They are different from a simple diagnostic scan in several important ways. When a scan is to be used for radiation treatment planning, the patient must be scanned in a precise position that will be repeated in subsequent radiation therapy sessions under the linear accelerator. This position simulates the treatment position and therefore is determined by the radiation oncologist. The simulation scan is extremely important because it serves as a template for delivery of radiation throughout the course of treatment. Because the patient will be expected to assume this same position before receiving each of the 25 to 40 fractionated doses over the course of 4 to 6 weeks, the precise, rapid reproducibility of this position is critical to assure accurate delivery of the total prescribed radiation. To limit variations in position, immobilization of the patient for both the scan and the subsequent therapy are performed using a flat table and immobilization devices that are customized to each patient (conforming body casts, thermoplastic face masks, head holders, belly boards). Lasers are used to guide the marking of the patient's skin. Using a laser in a transverse plane at a level corresponding to the bulk of the tumor, three fiducial markers are placed to establish a reference slice within the CT data. Within this slice, a reference point called a pseudo iso-center focused on the tumor is established. From this reference point, the precise target is identified and as necessary this point is shifted to a 'true' iso-center. Consistent spacing of the CT slices is required. Diagnostic as well as simulation CT scans of the neck typically use a slice thickness of 2 to 3 mm compared with a body scan, which is usually reconstructed in 5-mm increments. In the case of a simulation CT scan of the head and neck, the patient is usually immobilized in a thermoplastic mask, and the CT typically is about 40 s so that the patient tolerates the scan easily. However, when the PET portion of the scan is added, imaging time may approach 10 min, which can be uncomfortable for patients who may have difficulty with secretions. A total body PET scan should also be obtained in patients with head and neck squamous cell carcinomas because not infrequently patients also will have disease outside the neck or a second primary tumor, usually in the lungs.^{1,2}

When PET is added to any CT or MRI, fiducial markers are sometimes used to verify registration, particularly if the patient had to be moved between the PET and CT or MRI acquisitions. The planning software maybe asked to calculate a plan that factors in the heterogeneous CT densities particularly within the chest and, therefore, a noncontrasted CT may be required. Simulation CT scans and especially PET-CT scans need more setup time than diagnostic scans and may be more uncomfortable for patients because of the immobilization devices. Many patients require sedation. All PET patients are asked to fast for 4-6 h before the administration of FDG to enhance tracer uptake by tumor. All adult patients are asked to refrain from vigorous or strenuous exercise 48 hours before scanning to avoid physiologic uptake in recovering muscles. Also, all are

asked to wear warm clothing, particularly around the neck and shoulders, to prevent FDG uptake in brown adipose tissue of the neck and upper torso and also to prevent shivering and subsequent intercostal muscle uptake. In patients with difficulty controlling salivary secretions, atropine-like agents (Robinul 0.1 mg IM) may be administered. And in patients who have anxiety and/or are likely to become uncomfortable during imaging, benzodiazepines (diazepam 5 mg orally) are given at the time of FDG injection. In patients who are coughing, narcotics (codeine 5 mg orally) have been very effective. We discourage the patients from speaking or moving during the 60-90 mins of FDG uptake. Before scanning, all patients are asked to urinate. The immobilization devices are created under the instruction of the radiation oncologist. They are made based on the known location of the patient's tumor on scanning. For lung lesions, much work is being performed to address respiratory and cardiac movement of tumors. Registration problems between PET and CT and as well as target movement can be elegantly addressed with gating.³ In lieu of this, perhaps the most practical solution is for the patient to have a simulation CT of the chest during moderate end-expiration breath holds.⁴ This generally provides good registration between the PET and CT because with the PET scan there will be volume averaging and the longer end-expiration phase means the PET favors depicting the lesion in the end-expiratory phase. This represents a compromise for CT because smaller lesions are better seen with a breath hold during maximal lung expansion. Asking the patient to hold their breath after exhaling is more practical for planning and subsequent therapy. It is also easy for the patient to perform. For most patients, a high-quality diagnostic CT is performed using both oral and IV iodinated contrast. High-density objects may cause PET artifacts in PET-CT scanners, but these attenuation-correction artifacts are predictable and are a reasonable trade-off compared with the value of a high-quality CT.⁵⁻⁸ Once all of the data have been acquired, the simulation PET and CT image sets are sent to the radiation treatment software. Manufactures of radiation planning software must validate the DICOM compatibility of any CT or PET scanner before its data being accepted. The RTP manufacturer may assess scanner licensure fees. Once the PET and CT data sets have been acquired, they must be sent separately to the RTP system to be fused within the planning software. A prefused PET-CT image will not be accepted into most RTP systems (eg, Pinnacle, Philips). Once the two data sets are in the RTP software, they may require manual registration to become fused or an automated program may be available. The primary data set is the CT and the colorized PET images are subsequently superimposed on the CT.

Although the CT has set windows and centers that are optimized for displaying various tissue densities, the PET data requires subjective thresholding to eliminate background activity and to conform the PET intensity to a definite structure in the underlying CT.

Actual drawing of gross tumor volumes is better accomplished when viewing the fused PET-CT transaxial slice beside the CT alone. This allows the observer to take notice of the high-contrast fused image set for detection of lesions and at the same time use the CT to define tumor margins. PET images do not provide true edges; therefore, the underlying anatomical edge must be used as a guide to contour the tumor region of interest. When talking about drawing gross tumor volumes in our facility, we commonly say "PET finds it and CT defines it." Some exceptions occur where PET is used to define a tumor's edge by default, and these include a neck or pelvic mass that blends in with surrounding soft tissue or in a lung mass where the tumor's edge cannot be distinguished from accompanying atelectasis. An obvious tumor seen with CT that does not have FDG within it is still included in the gross tumor volume (GTV). In a study in our department of 14 patients with squamous cell carci-

noma of the head and neck, there was concordance between the CT and PET in 23 lesions, but PET found 18 additional lesions and CT showed 14 lesions that were not FDG-avid. Experienced interpreters of both CT and PET in our facility have decided that for a PET lesion to be included in the GTV, it must either correspond to an underlying CT abnormality, a lymph node, or have a convincing intensity within a common site for disease (eg, vertebral body) that cannot be explained by a benign process or artifact. The total GTV includes CT findings, PET findings, and known cancer from clinical findings or physical examination findings. The radiation oncologist then estimates the location of subclinical disease from knowledge of nodal basins, neurovascular paths, and any patient symptomology and then adds this extra area to the GTV. This is called the clinical target volume (CTV). The planning target volume (PTV) is equal to the CTV but with two more layers added (the internal margin which considers organ movement and the setup error that takes into account errors associated with positioning a patient). Collectively, the GTV, CTV, and the PTV resemble an onion with the final volume known as the PTV.⁹ Therefore, the PTV is much larger than the GTV.

Next, optimization software designs beam paths based on the CT scan. Because external beam radiation directed to a tumor will also encounter surrounding normal tissue, a multidimensional radiation therapy plan must strike a balance between delivering a tumoricidal dose to the target while imposing constraints on how much radiation is allowed to fall on uninvolved tissue. For example, a plan for irradiation of a head and neck tumor may be prescribed to deliver 70 Gray but place constraints such that inadvertent radiation to the adjacent spinal cord be limited to 45 Gray, 50 Gray to the eye, and 45 Gray to the mandible. Therefore, for the RTP software to function, PET alone is insufficient and anatomic imaging modalities such as CT or MRI must map out the normal tissue. At this time, PET in conjunction with CT is used qualitatively to target tumors and a conservative approach is usually taken that does not modify targeting based on the PET intensity within the GTV.

Clinical Applications

Lung Carcinoma

Lung carcinoma is one of the most lethal of all carcinomas and, excluding skin cancer, it is the second most common malignancy of men and women behind prostate and breast, respectively. The overall 5-year survival of patients diagnosed with lung carcinoma is approximately 14%. Only one third of presenting patients are eligible for curative-intent surgery.¹⁰ Small cell lung carcinoma (SCLS) is considered a systemic disease and although chemoradiation for local disease is a consideration, chemotherapy is the mainstay of treatment.¹¹ In nonsmall cell lung carcinoma (NSCLC), patients with no involved lymph nodes (N0) or only positive hilar nodes (N1) may have operable disease if the primary tumor is judged to be resectable.¹² In the patients who have limited disease but are nonoperable candidates, definitive radiation using 60 to 80 Gray may be used. Because the brain is a common site for recurrent disease in both NSCLC and SCLS, prophylactic brain irradiation (30 Gray) may be indicated.¹³ For the radiation oncologist, the role of PET is for staging, tumor targeting, and restaging of the disease. Confidence in PET accurately staging lung carcinoma derives from its high sensitivity 95% and specificity 81% for detecting carcinoma in lung nodules.¹⁴ Also, because radiation frequently follows surgery, accurate targeting in the mediastinum is critical and PET provides this with a sensitivity and specificity for mediastinal nodal disease of 88% and 91%, respectively.¹⁴ PET offers a very high negative pre-

dictive value for mediastinal involvement (91% to 97%).¹⁵⁻¹⁸ Finally, PET provides a whole body image, thus giving one a greater opportunity to detect the most common sites of distant metastatic disease, such as the liver, adrenal gland, and bone. (For the brain, MRI is the preferred modality to assess metastatic disease.) In a study of 50 adrenal lesions, the sensitivity, specificity, and accuracy of PET was 100%/94%/96%, respectively.¹⁹ Disease upstaging with PET is common and in a study by Valk and coworkers of 99 patients, 11 demonstrated distant disease undetected by prior conventional imaging.²⁰ In our institution, 37 of 113 patients with NSCLC were discovered to have metastatic disease outside the mediastinum. Changes in treatment usually resulted in less aggressive radiation planning or redirecting therapy to new sites such as the spine or femur. A prospective study of 105 consecutive patients with NSCLC showed that the addition of PET changed management from curative to palliative intent in 26% of patients and changed overall management in 67%.²¹ In a large study of 153 patients with NSCLC, PET changed the stage of 33% of the patients and changed the target volumes for radiation in 25%.²² PET also plays a role in detecting recurrent disease. Scarring and postoperative changes complicate anatomic interpretation of images and needle biopsy returns an indeterminate result up to 30%.²³ In patients who were status-post treatment for NSCLC, PET has an accuracy between 78% and 98%.²⁴ Because postradiation pneumonitis and inflammation are more common immediately after treatment, increasing the interval between the end of radiation therapy and the PET scan provides a greater specificity for abnormal findings. In timing the posttreatment PET scan, 4 to 6 months is best.¹⁴ Our earliest recommendation is 6 weeks. (Note: Postradiation inflammation has been seen by this author at 18 months after therapy.) Combined PET-CT has been extremely helpful in eliminating false-positive interpretations of the PET scan in patients who have obvious postradiation changes and helps the interpreter to explain FDG uptake that does not correspond to a suspicious structural lesion. For example, within the radiation field, focally intense activity in lung adjacent to a dense scatter-causing structure, eg, aortic arch may be explained by the higher amounts of radiation that it received throughout therapy. Also, knowledge of the radiation fields can help explain why similar tissue may have variable tracer uptake. Finally, some studies have indicated that the intensity of the FDG uptake within the lung tumor represents an independent risk factor for recurrence with staging standardized uptake values (SUVs) >7 to 10 showing shorter survival in patients.¹⁴

Head and Neck Carcinoma

In the United States, head and neck carcinoma are the seventh and eleventh most common carcinoma in men and women, respectively.¹⁰ Head and neck carcinoma is the most common indication for an "RTP simulation" PET-CT scan in our facility. This is because for most cases radiation is at least equivalent to surgery and preserves a greater degree of function.^{25,26} Head and neck carcinoma patients in our center usually receive intensity-modulated radiation therapy that directs highly concentrated radiation to small areas and thus accurate targeting is required more than ever. More than 90% of head and neck carcinomas are squamous cell carcinomas and radiation therapy or chemoradiation frequently is used as first-line treatment followed by elective neck dissection. Adenoid cystic carcinoma and salivary adenocarcinomas also are indications for radiation therapy. Ulceration of the surface mucosa in the mouth or pharynx is the most common presentation and the most commonly involved lymph node is a jugulodigastric node. Infiltrative or endophytic growth may not be clinically visible even with endoscopy,

CT, or MRI, and in such cases PET has been found to determine a site of origin in ~60%.²⁷ For all stages, the 5-year survival is approximately 50%. Of patients for whom therapy fails, 90% will have recurrent disease within the first 2 years after treatment. The median survival of patients with local or metastatic recurrent disease is 6 months.¹⁰ Staging the neck alone with various imaging modalities shows the following sensitivities and specificities: PET 70% and 82%; CT 66% and 74%; MRI 64% and 69%; ultrasound 84% and 64%.²⁸ Overall, PET-CT is likely the modality of choice; however, no modality has the capability of detecting micrometastatic disease. In a study²⁹ of 12 patients with oropharyngeal squamous cell carcinoma who demonstrated no physical or radiologic findings to suggest nodal metastasis, a PET scan was obtained that showed two patients with nodal metastases. All 12 patients then underwent subsequent surgery with sentinel node biopsy, followed by elective neck dissection. Pathology revealed 5 of the 12 patients had nodal metastasis. Mean size the nodal metastases, was 1.4 mm (range, 1.2–1.5 mm). The PET scan detected only one patient with a metastasis of 12, with the other patient having a false-positive scan. Consequently, planning radiotherapy and surgical approaches must be cognizant of the limitations with PET. What this translates to for the radiation oncologist is that even with PET, one must not only consider the GTV but also must continue to estimate subclinical involvement (the CTV). Subclinical disease usually is lymphatic or perineural invasion and by lowering the upper threshold of the PET data this can occasionally be detected. Experience and care must be exercised when interpreting FDG uptake in the pharynx because of variable physiologic activity in the base of the tongue, posterior nasopharyngeal and oropharyngeal walls, cricoid and arytenoid cartilage, plus salivary pooling in the piriform recesses. Also, most patients have inflammation from tooth extractions required before radiation. PET scanning has a role in assessing neoadjuvant or induction chemotherapy but is generally not obtained during concurrent chemoradiation. PET scans obtained during radiotherapy typically show increased FDG uptake in tumors, early in the course of radiation therapy (<20 Gray), and decreased activity near the end of therapy (>45 Gray).³⁰ The inflammatory activity observed in surrounding normal structures usually return to baseline by 6 weeks, with the exception of cartilaginous tissue. In some cases, postradiation inflammation can be observed for several months. The accuracy of PET was highest—94%—in patients who were scanned more than 3 months after the end of radiation therapy.³¹ PET also can assess adjuvant chemotherapy after loco-regional (surgery or radiation) control if the scan is obtained at least 6 weeks after radiation. The sensitivity of FDG PET for detection of recurrent disease is 90%, with 83% specificity and patients who had complete remission of their tumor had a mean reduction of FDG uptake of 82%.³² In both lymph nodes and irradiated tumor with activity levels > 3 mg/mL (SUV max 3) are qualitatively called positive and are suspicious for recurrent disease.³³

Lymphoma

Lymphomas are divided into Hodgkin's disease (12%) and non-Hodgkin's lymphomas (88%).¹⁰ In our facility, PET has taken the place of gallium scans for staging and detection of recurrent disease because PET has better sensitivity and spatial resolution.

In Hodgkin's disease, the disease process tends to be unifocal in origin and the pattern of progression is contiguous lymphatic spread at the time of presentation and also in cases of relapse. Therefore, patterns of involvement in Hodgkin's disease are more predictable than in non-Hodgkin's lymphomas. In 60% to 80% of patients, there is lymph node involvement in cervical or supracla-

vicular regions.¹⁰ Chemotherapy alone, irradiation alone, or chemotherapy and irradiation are effective. Today, the effectiveness of combination chemotherapy and the desire to avoid the adverse late effects of radiation means radiation often is used for consolidation treatment after chemotherapy.^{34,35} In patients with bulky disease, simulation PET-CT scans are performed in patients particularly those with a large mediastinal mass. With PET in Hodgkin's disease, uptake of FDG by the tumor tends to be quite high, offering excellent contrast resolution. PET scan sensitivity, specificity, and accuracy for staging Hodgkin's disease are 88%, 100%, and 90%, respectively. For therapy monitoring and determining residual tumor, its sensitivity, specificity, and accuracy are 85%, 96%, and 96%.³⁶

In patients with non-Hodgkin's lymphoma, noncontiguous spread of the disease is common with skin, gastrointestinal tract, bone, and Waldeyer's ring more commonly involved than in Hodgkin's disease. The mediastinum frequently is spared in non-Hodgkin's lymphoma. Immunotherapy, radiation alone, surgery, combined chemotherapy with radiation, or even no therapy all can be used as initial treatment strategies depending on the patient, the particular cell type, and the stage. Radioimmunotherapy (Zevalin and Bexxar) is now an option for disseminated recurrent or persistent disease. Overall recurrence rates in patients with non-Hodgkin's lymphoma are greater than 50%. FDG uptake tends to be highest in clinically aggressive lymphomas. Mucosa-associated lymphoid tumor lymphomas have high cellularity and tend to be of low grade and thus can have minimal FDG uptake. Consequently, overall sensitivity of PET for non-Hodgkin's lymphoma is more variable compared with Hodgkin's, and PET has a lower sensitivity (83%), specificity (100%), and accuracy (86%) for staging. However, if the baseline study demonstrated tumor uptake, monitoring therapy for residual disease has an accuracy near 100%.³⁶ In both Hodgkin's and non-Hodgkin's lymphoma, follow-up PET scans can not exclude the presence of residual disease nor can they predict complete remission.³⁷

Rectal Carcinoma

Colorectal carcinoma is the fourth-leading cause of cancer mortality. Seventy percent of the tumors are considered resectable, but one third of postoperative patients will go on to have a recurrence typically within 2 years of resection. Overall 5-year survival rate is 61%.¹⁰ Resection of the tumor is preferred with adjuvant radiation used either preoperatively or postoperatively and usually combined with chemotherapy.³⁸ Compared with surgery alone, patients who received postoperative radiation demonstrated a decrease in local relapse from 25% to 16%.¹⁰ Preoperative chemoradiation is the recent trend in hopes of downstaging the disease to enhance sphincter preservation and to decrease other toxicities such as small bowel injury or anastomotic structures.³⁹ Current Medicare guidelines require a rising carcinoembryonic antigen or a CT mass as a criterion for ordering a PET scan. Unfortunately, carcinoembryonic antigen is only 59% sensitive and 84% specific for recurrent disease.⁴⁰ Meta-analysis show the sensitivity and specificity of PET for recurrent colorectal carcinoma is 97% and 76%.⁴¹ PET-CT also has a role in newly diagnosed patients referred for adjuvant radiation who have suspicious lymph nodes in the pelvic sidewall; here, a PET-CT scan may be very valuable for radiation treatment planning. Because most relapses will be in the posterior one half to two thirds of the true pelvis, the internal iliac and presacral nodes are suspect from the beginning. Also, in advanced stages of the disease, targeting of the sacral canal with 40 to 50 Gray may be necessary to prevent tumor spread along the nerve roots. Diagnostic and pretreatment PET-CT scans may require prone imaging and rectal or urinary

catheters to separate the tumor from the bladder and other structures. When interpreting PET scans, it is helpful to know that tumors originating in the upper rectum have venous drainage via the superior hemorrhoidal veins to the inferior mesenteric vein, to the portal vein, and subsequently into the liver. Lower rectal tumors drain to the internal iliac, to the inferior vena cava, and subsequently into the lung. Lesions that extend into the anus or vagina may have inguinal lymph node drainage.

Cervical Carcinoma

Radiation therapy with concomitant chemotherapy is the standard of care for all advanced stages of cervical carcinoma. Surgery is limited to stage I to IIA or recurrent disease.⁴²⁻⁴⁴ Cure rates for stage I are 85%, stage II are 65%, stage III are 45%, and stage IV are 25%.¹⁰ External beam therapy with or without intracavitary radiation or seeds may be administered, and radiation is the treatment of choice for locally advanced disease. Like rectal carcinoma, the evaluation of pelvic lymph nodes—internal iliac and presacral nodes—are critical. PET outperforms CT and MRI in the evaluation of pelvic nodes with a sensitivity, specificity, and accuracy of 83%, 92%, and 88%, respectively.⁴⁵ Positive nodes on PET should have extended field radiation therapy. In evaluating recurrent disease, a biopsy is often not practical, but abnormal uptake on PET correlates with a shorter 2-year disease-free survival compared with those with no abnormal finding (40% versus 86%).⁴⁶ Repeat radiation therapy for recurrent disease in these cases is often for palliation only and not for salvage.

Esophageal Carcinoma

Esophageal carcinoma patients have a poor long-term survival. The treatment of choice is esophagectomy for stages 0, I, or IIA. The 5-year survival of these patients is only 22%. For patients who are not surgical candidates, including those with high esophageal lesions and in patients with advanced stages, chemoradiation is the therapy of choice.¹⁰ Preoperative radiation commonly is employed. Because the diagnosis is made by esophagoscopy, descriptions such as “a fungating lesion biopsied 25 cm from the teeth” may not be very helpful to a radiation oncologist attempting to target the lesion using a CT scan. Furthermore, these tumors tend to spread submucosally usually 5 cm beyond visibly gross tumor. Because PET frequently shows the greater extent of the tumor, including multiple skip areas plus distant disease and to a lesser degree nodal involvement, it is the preferred modality for staging. PET does suffer from a lack of specificity in the esophagus because of salivary secretions and physiologic activity, particularly in the gastroesophageal junction and stomach. Approximately 40% of carcinomas are of squamous cell type, and approximately 60% are adenocarcinomas, particularly those in the distal esophagus. Rarely do oat cell carcinomas, sarcomas, and melanoma present. Gastroesophageal junction tumors typically spread to mesenteric nodes, whereas upper esophageal lesions tend to spread to cervical nodes. The status of regional node involvement is the most important prognostic factor. Unfortunately, although PET has high sensitivity and specificity for disease within the esophagus with a sensitivity of 90% to 100%, the sensitivity, specificity, and accuracy of PET for locoregional nodal metastasis was only 45%, 100%, 48%, respectively.^{47,48} For distant metastatic disease PET is better with a sensitivity between 70% and 100% and a specificity of 94%.⁴⁷ For recurrent disease within the esophagus after therapy, the sensitivity, specificity, and accuracy is 100%, 57%, and 74%, respectively.⁴⁹ The lack of specificity for recurrence was perhaps caused by strictures and focally intense activity after radiation or in anastomotic segments. Consequently,

when planning for radiation therapy, the low sensitivity of PET for detection of local nodal disease must be taken into account by the radiation oncologist.

Perspectives and Future Trends

A PET tracer with high accuracy in detecting prostatic carcinoma would greatly further the use of PET in the radiation oncology community. Currently, it has been PET-CT scanners that have introduced radiation oncologists to the world of PET. As new scanners increase resolution and sensitivity, upstaging of cancer will continue. Consequently, management with radiation often changes to being either less aggressive and/or additional sites being treated. Just what effect the addition of PET to CT in radiation therapy planning has can only be determined with prospective studies of patients. Patients with a similar pathology and stage of disease must be randomized into those who do or do not have a PET scan added to their RTP, must be treated in a similar fashion, and must be followed at similar intervals. Such studies are very difficult to conduct because there are so many variables in cancer patients, not the least of which is the microscopic or unseen differences in similarly staged patients. Another variable is that radiation therapy regimens often include chemotherapy. The rapid changes in technology associated with the delivery of radiation also affect any longitudinal studies. For example in only 4 years, the imaging equipment in our facility has changed from a separate NaI PET and CT scanner connected by software to a dedicated BGO PET/dual-slice CT to now an LSO PET/16-slice CT scanner. Additionally, in our cancer center, the linear accelerator has been upgraded with intensity-modulated radiation therapy collimation and gating software, and soon a completely new tomographic linear accelerator will be added. Despite the lack of data, the most unequivocal evidence that PET is beneficial has been its rapid adoption by the oncology community as a whole. As the modality matures caveats of clinically significant information will emerge. One piece of information that is being discovered is that PET-CT exceeds the sensitivity specificity and accuracy of PET alone. In a study by Haney and coworkers in which patients with a wide variety of malignancies were studied, PET-CT demonstrated sensitivity, specificity, and accuracy of 98%, 99%, and 98%, respectively, compared with PET alone, where the sensitivity, specificity, and accuracy were 90%, 93%, and 91% respectively.⁵⁰ Also, combined PET-CT allows readers to factor in the size of a suspicious PET focus. In PET alone, lesions called “positive” qualitatively must have a high degree of contrast to the human eye. Quantitatively, this translates to SUVs or tumor to background ratios of greater than 3:1 or 3 mg per milliliter. However, the measured activity in a mass depends in part on its size. Small tumors less than twice the spatial resolution of the PET scanner will typically have underestimated activity. Because most PET scanners have a spatial resolution of approximately 7 mm after filtering, quantitative accuracy can only be assured in lesions 1.4 cm in size or greater. Therefore, experienced PET-CT interpreters in our center feel that small lymph nodes with even low-level activity are suspicious. In all cases it is always helpful to know the relative PET intensity of a biopsy-proven tumor at diagnosis. If the known tumor demonstrates low level FDG uptake, proportionally lower thresholds can be adopted for calling other lesions “positive,” particularly if the CT is suspicious. This affords greater sensitivity with minimal loss of specificity.

Some studies claim patients with carcinomas that have a high FDG uptake have a poorer prognosis and that this is an independent risk factor. However, prognosis is only relative to the effectiveness of treatment. For example, some tumors, such as seminoma and

Hodgkin's disease, are extremely FDG-avid but they are usually treated successfully and have good prognoses. Conversely, pancreatic and renal cell carcinomas often have low FDG uptake but have poor outcomes. Current treatment is under constant change for those patients with a poor prognosis malignancy. Such patients, if they meet admission criteria, are often enrolled in clinical trials using novel drugs or regimens. An important use of PET for the oncology patient is to evaluate early treatment response to chemotherapy. If a tumor had a high baseline activity and maintains high FDG uptake during or after treatment, the tumor should be considered viable and the current therapy is considered to be ineffective. Likewise, for radiation therapy, hopefully, future studies will show us whether radiation focused on the most intense FDG-avid tumors will have a favorable impact on local control. Autoradiographs show that FDG intensity correlate with hypoxic areas within a malignancy.⁵¹ Because hypoxic areas are radio-resistant, it follows that focused radiation to these areas should mean better local control.

At this time, PET and the physics behind it are somewhat new to the radiation oncology community, and methods to even validate PET data in treatment plans are not fully established.⁵² Also, software applications to best use PET for targeting tumor within the available treatment plans are evolving.⁵³

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